



Awake brain surgery in children—review of the literature and state-of-the-art

Laura-Nanna Lohkamp¹ · Carmine Mottolese¹ · Alexandru Szathmari¹ · Ludivine Huguet¹ · Pierre-Aurélien Beuriat^{1,2} · Irène Christofori² · Michel Desmurget² · Federico Di Rocco¹

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Abstract

Objective Awake brain surgery (ABS) is poorly reported in children as it is considered having limited indications due to age and neuropsychological aspects interfering with its feasibility and psychological outcome. The aim of this article is to review the current state-of-the-art of ABS in children and to offer an objective summary of the published literature on diversified outcome aspects of pediatric awake procedures.

Methods A literature review was performed using the MEDLINE (PubMed) electronic database applying the following MeSH terms to the keyword search within titles and abstracts: “awake brain surgery children,” “awake brain surgery pediatric,” “awake craniotomy children,” “awake craniotomy pediatric,” and “awake surgery children.” Of the initial 753 results obtained from these keyword searches, a full text screening of 51 publications was performed, ultimately resulting in 18 eligible articles for this review.

Results A total of 18 full text articles reporting the results of 50 patients were included in the analysis. Sixteen of the 18 studies were retrospective studies, comprising 7 case series, 9 case reports, and 2 reviews. Eleven studies were conducted from anesthesiological (25 patients) and 7 from neurosurgical (25 patients) departments. Most of the patients underwent ABS for supratentorial lesions (26 patients), followed by epilepsy surgery (16 patients) and deep brain stimulation (DBS) (8 patients). The median age was 15 years (range 8–17 years). Persistent deficits occurred in 6 patients, (12%), corresponding to minor motor palsies (4%) and neuropsychological concerns (8%). An awake procedure was aborted in 2 patients (4%) due to cooperation failure and anxiety, respectively.

Conclusions Despite well-documented beneficial aspects, ABS remains mainly limited to adults. This review confirms a reliable tolerability of ABS in selected children; however, recommendations and guidelines for its standardized implementation in this patient group are pending. Recommendations and guidelines may address diagnostic workup and intra-operative handling besides criteria of eligibility, psychological preparation, and coordinated neuropsychological testing in order to routinely offer ABS to children.

Keywords Awake brain surgery · Children · Pediatric neurosurgery · Neuropsychology · Outcome

Introduction

The principle of awake brain surgery (ABS) evolved since the first maps of the sensory and motor cortices of the brain have

been developed by Wilder Penfield [1]. The initial purpose of ABS was to correlate functional and pathological areas throughout epilepsy surgery while stimulating different areas of the cortex. Later on, this principle was translated to tumor surgery and generated the basis for today’s awake procedures applied as a standardized approach, aiming to increase tumor removal while preserving neurological functions [2, 3]. Allowing seizure control besides minimizing operative morbidity made ABS a common intervention in adults for either intrinsic brain tumors, notably low-grade glioma, or distinct lesions in eloquent areas. The overall outcome of ABS in adult patients, including morbidity, mortality, treatment conditions, and neuropsychological aspects, has been widely studied and

✉ Laura-Nanna Lohkamp
laura-nanna.lohkamp@sickkids.ca

✉ Federico Di Rocco
Federico.Dirocco@chu-lyon.fr

¹ Department of Pediatric Neurosurgery, Hôpital Femme Mère Enfant, Université Claude Bernard Lyon 1, Lyon, France

² Center for Cognitive Neuroscience, Lyon, France

reported in several patient cohorts [4–7]. Some of these studies were performed as randomized or multicenter trials in order to report relevant patient numbers of more than a few hundred [4, 6, 8]. More importantly, the results of these and other studies have been predominantly positive, especially in terms of preserving neurological function, extent of tumor resection, and perioperative complication rate, all of them increasing overall survival [6, 9–11]. Despite these results, being observed in adult patient cohorts and underlining the beneficial aspects of ABS, comparable observations within the pediatric population remain pending [12–14]. While ABS became a standard of care in adults, equivalent translation of ABS to pediatric patients is withheld due to an assumed increased psychological fragility in children and age-related cooperation capacity interfering with feasibility and psychological outcome [12, 15]. However, few reports on ABS in children do exist, and this article aims to summarize these in addition to deriving a probable state-of-the-art for ABS in this specific patient group. This article will equally comprise studies conducted from a surgical and from an anesthesiological point of view. Furthermore, it aims as a literature review, to consider any outcome aspect of ABS in children, including methodical, surgical, and psychological factors differing from those of adult patients.

Methods

Search method

A systematic review of the entire MEDLINE database was performed through PubMed interface in order to identify relevant abstracts and articles. The following search terms were used for screening of titles and abstracts: “awake brain surgery” and “children,” “awake brain surgery” and “pediatric,” “awake craniotomy” and “children,” “awake craniotomy” and “pediatric,” and “awake surgery children.” Bibliographies of all selected articles were consecutively reviewed for identifying additional relevant studies. Of the initial 753 results obtained from these keyword searches, a full text screening of 50 publications was performed, ultimately resulting in 18 eligible articles for this review. There were no limitations concerning the subspecialty, which provided the article.

Inclusion criteria

Articles (prospective and retrospective studies) written in English and reporting on outcomes specific to ABS in children and adolescents below the age of 18 years were reviewed. All neurosurgical procedure types and indications using protocols of ABS were included. Outcomes could be related to anesthesiological, surgical, neurological, and neuro-psychological factors. Conversely, exclusion criteria were

studies that did not concern the specific age group or reported pediatric outcomes within an adult cohort, where the individual data of the included children were not selectable from the results. Studies using anesthesiological protocols for awake surgery in non-neurosurgical procedures were also excluded from this review. Duplicate studies were defined as those including outcomes on a previously reported population; however, if the study included additional patients or information such as consecutive follow-up data that were separately described, the information was included.

Identified studies

Seven hundred fifty-three studies were initially identified throughout the abovenamed keyword searches. Seven hundred two were excluded at the title and abstract screening because they did not meet inclusion criteria. The 51 remaining studies were considered for a full text screening, of which 33 did not meet the inclusion criteria or did not provide sufficient information on the single patients, qualifying 18 studies being relevant for the present review (Tables 1 and 2).

Objectives

The primary objectives were to assess the overall frequency and outcome of ABS in pediatric patients. Outcome refers in this review to neurological and neuropsychological criteria and differentiates between transient and permanent deficits. The secondary objectives were to determine the context of ABS in children and the circumstances in which ABS failed.

Results

Reporting results

The results of the 18 studies, which have been included in this review, are reported either from a neurosurgical (7 studies, 25 patients) or from an anesthesiological (11 studies, 25 patients) perspective. The 7 neurosurgery-derived studies included 4 case series, 2 case reports, and 1 review [12–19]. The anesthesiological-derived studies comprised 2 case series, 8 case reports, and 1 review [20–28]. All studies in both groups were retrospective, non-randomized ones and reported in total 50 pediatric patients, who underwent distinct neurosurgical procedures within an awake craniotomy protocol.

Patient data and perioperative assessment

Varying data of 50 distinct children were reported in the different studies. Gender information was available in 41 patients, representing a male to female ratio of 24 to 17 patients. The exact age was available from 38 children, resulting in a

Table 1 Summary of neurosurgical studies included in this review indicating context, patient numbers, and outcome of the studies

Author	Year	Patient numbers	Context	Median age (years)	Failure of ABS	Transient/permanent neurologic deficits	Transient/permanent neuropsychological deficits
Air et al.	2011	6	DBS	Unknown	0	Not validated	Not reported
Akay et al.	2015	2	STL	13.5 (12; 15)	0	1/0	0/0
Balagoun et al.	2014	10	STL (7); E (3)	15.5 (11–17)	1	1/0	Not reported
Delion et al.	2015	6	STL	13.5 (11–16)	0	4/0	2/4
Klimek et al.	2004	1	STL	9	0	0/0	0/0
Requin et al.	2017	7	STL	12 (8–16)	0	4/0	2/4
Requin et al.	2017	1	STL	8	0	0/0	0/0
Trevisi et al.	2016	0	Review				

calculated median age of 15 years (mean age 13.8 years). Four children among the 50 patients were under the age of 10 years, with the 2 youngest being 8 years old [19, 23]. Concerning pre-operative imaging, information was available in all studies that were performed from a neurosurgical perspective and partly from the anesthesiological studies. Functional MRI was performed pre-operatively at least in 26 of the patients. Hemispheric dominance was indicated in 22 of the 50 patients, showing a right to left ratio of 14 to 8. Information on neuropsychological workup could be retrieved from 43 patients and included confirmation of pre-operative assessment in 34 and post-operative assessment in 9 patients, respectively.

Neurosurgical procedure

Indications for surgery were insertion of DBS electrodes (8 patients), supratentorial lesions of varying entities (26 patients), and epilepsy surgery (16 patients) (Tables 1 and 2). The specific indication for ABS was related to the location of the lesion, respectively the epileptogenic foci, in an eloquent region. The surgical procedure was in all of the cases conducted as an asleep-awake-asleep protocol and conducted

with intra-operative electrocortical mapping except for DBS insertion [16]. Variations were found in the anesthesiological management, including different drugs and ventilation methods. For example, Ard et al. reported the first pediatric patient group, in which sedation with dexmedetomidine was applied during ABS, followed by 2 similar case reports of Maurtua et al. and Sheshadri et al. [20, 23, 25], whereas in most of the other cohorts propofol sedation was used.

Failure of ABS was documented in 2 of the total 50 reviewed patients due to combative and uncooperative behavior and anxiety, respectively. Both conditions necessitated interruption of the awake phase [17, 23].

Intra-operative complications occurred in 2 patients. One suffered from apnea and required intubation [17], whereas another patient experienced venous air embolism, leading to abortion of the procedure [29].

Consistent information on intra-operative presence of a neuropsychologist and the use of any other additional devices, such as navigation, or ultrasound were not available from all of the studies. However, the major neurosurgical case series applied navigation or stereotaxy [15–17], and 2 studies reported additional use of intra-operative ultrasound to confirm the

Table 2 Summary of anesthesiological studies included in this review indicating context, patient numbers, and outcome of the studies

Author	Year	Patient numbers	Context	Age (mean)	Failure of ABS	Complications	Transient/permanent neurologic deficits
Ard et al.	2003	2	STL	xxx	0	None	Not reported
Everett et al.	2006	2	STL	16	0	None	0/0
Gooden et al.	2010	1	DBS	9	Due to complication	Venous air embolism	0/0
Hagberg et al.	2004	3	STL (1); E (2)	13	0	None	0/0
Klimek	2004	1	STL	9	0	0/0	0/0
Maurtua et al.	2009	1	DBS	8	0	None	0/0
Mc Clain et al.	2014	0	Review				
Sheshadri et al.	2016	1	E	11	0	None	0/0
Soriano et al.	2000	12	STL (2); E (10)	13	0	Generalized seizure; stroke	0/1
Sung et al.	2010	1	STL	16	0	Right facial nerve palsy	0/1
Tobias et al.	1997	1	STL	12	0	None	0/0

completion of resection [14, 17]. Neuromonitoring, such as SSEP, MEP, and EMG, was conducted as supplemental measure in 2 studies [17, 27]. Intra-operative hypnosis conditioning was reported and applied in 5 procedures for anesthetic induction, perioperative awakening, and during periods without stimulation [13, 15, 19]. In the same study, 4 patients were reported to have had the chance to meet another child who had been operated on by a craniotomy while awake to explain her psychological experience in addition to presentation of visual material representing the atmosphere of the operating room [13].

Clinical outcome

Overall, awake procedures were psychologically well tolerated by 48 out of 50 children, including 3 patients under the age of 10. Failure of awake brain surgery due to combative and uncooperative behavior was reported in a 13-year-old patient and an episode of anxiety during the awake phase in an 8-year-old boy, both necessitating abandonment of the awake phase [17, 23]. A 17-year-old female developed intra-operative apnea requiring airway securing and equally interruption of the awake phase, whereas the entire surgery needed to be withdrawn in a 9-year-old child that experienced an anesthesiological complication, notable venous air embolism [29]. Another intra-operative complication, however not affecting the continuation of the awake episode, was a generalized grand mal seizure lasting greater than 20 s during electrocortical stimulation [26].

Post-operative deficits, which were described in the studies, were referred to neurological and neuropsychological deficits. Furthermore, they were classified as transient or permanent deficits. As far as reported, post-operative neurological deficits were observed in 8 children, six of them showing transient and 2 permanent deficits. One patient developed a permanent hemiparesis after uneventful intra-operative testing and tumor resection, consistent with a stroke [26]. Another 16-year-old boy suffered from permanent right-sided facial palsy after resection of a left temporal glioma with extent to the somatosensory and the motor areas [27]. Minor transient neurologic deficits, such as focal epileptic seizures post-operatively in the first week in the form of aphasia [14] and worsening of a pre-existing word-finding disturbance, were reported in 1 patient each and got resolved over time [17]. Delion et al. reported 4 patients experiencing transient neurologic deficits after surgery. One patient showed moderate dysarthria and a partial right brachial and facial palsy, of which both improved rapidly during the rehabilitative course. Another patient suffered from additional algodystrophy while maintaining her pre-operative right hemiparesis and proprioceptive troubles. Further neurologic alterations, such as post-operative hydrocephalus requiring ventriculoperitoneal shunt

insertion and transient facial palsy with right-sided proprioceptive disorders, occurred in 1 patient each [15].

Information on the extent of resection was available from 4 studies, which included supratentorial lesion resections. Gross total resection was achieved in 15 out of 18 patients [14, 15, 17, 21]. Three children showed tumor residual on post-operative MR imaging and 1 of them required a second intervention. The other 2 patients had speech arrest during mapping, and thus subtotal resection was performed in order to spare language [15, 17]. Notably, 2 children were diagnosed with a relapse of their known tumor, one within 1 year and one within 18 months after ABS, and underwent repetitive awake brain surgery [15].

Neuropsychological outcome

Neuropsychological results were reported in 6 studies, 20 patients respectively, of which 2 experienced transient and 4 patients persisting neuropsychological deficits. However, none of the children showed symptoms of post-traumatic stress disorder (PTSD) or acute stress. Transient deficits, such as word-finding problems and a minor episode of depression, not requiring psychotropic medication, were observed in 1 patient each. One child, who had symptoms of depression just after surgery, required psychotherapeutic follow-up for 6 months. However, the depression was principally linked with the fear of a tumor relapse and not to the experienced surgery itself. Continuing difficulties with working memory or word-finding problems were documented in long-term follow-ups in 4 patients [13, 15].

Discussion

In this review, we summarize the results of 18 studies from distinct departments documenting their experience from different perspectives within ABS in 50 pediatric patients. Despite the beneficial aspects and well-documented reliable outcome results of ABS in adults [4, 5, 8–11, 30], its application in children remains scarce and still represents a major challenge for interdisciplinary teams [12, 24]. Thus, this review, integrating all reported interventions and their related aspects, aimed to derive recommendations and guidelines addressing specific aspects of this complex intervention in children. Results were analyzed with respect to epidemiologic data, pre-operative diagnostic workup, intra-operative application of technical supplies, and clinical and neurological outcome, respectively. In addition, attention was paid to the neuropsychological algorithm if applied, i.e., time-related assessment and intra-operative support of the patients. This review demonstrates both a summary of the prior reported results in pediatric awake brain surgery and the

remaining challenges as well as corresponding recommendations for their anticipation.

Clinical benefit and diagnostic prerequisite for ABS

The relationship between clinical benefit and the extent of tumor resection is highly predicated on the balance between tumor reduction and neurological morbidity [31]. Thus, independent from the patients' age, the purpose of ABS with electrocortical mapping is to minimize neurological morbidity while performing the best possible cytoreduction within eloquent areas [9, 32, 33]. Accordingly, all of the herein reported resection results confirmed successful gross total resection of supratentorial tumors and epileptogenic foci in close proximity to functional areas guided by intra-operative electrocortical mapping and eventual neuronavigation [15, 17, 25]. Gross total resection, as far as reported, was achieved in fifteen of 18 patients; in 2 patients, the resection extent was limited by surgical decision-making due to functional area involvement as indicated by electrocortical stimulation and neuronavigation [17]. Only one patient required reoperation for residual tumor [15]. Post-operative neurologic alterations were observed in 8 out of 50 patients (16%), six of them showing transient and 2 permanent deficits. However, the persisting deficit of one of the latter patients, who underwent uneventful intra-operative testing and tumor resection, was related to a vascular complication, notably a stroke [26]. Given these results, which correlate with results from adult cohorts [4, 34], the reliability and utility of the awake technique in order to maximize resection extent while minimalizing neurologic impact can be equally confirmed in children.

Pre-operative diagnostic workup of the patients was variable and included functional MRI, conventional MRI, or assessment of the dominant hemisphere via the WADA test. In few patients, two or more diagnostic modalities, including magnetoencephalography (MEG) or PET CT, were applied in a combined fashion. Although differences between the distinct modalities in terms of accuracy and impact on the individual surgical planning were not reported in the reviewed studies, the diagnostic superiority of functional MR imaging, including its use for neuronavigation, advocates it as a standard procedure for ABS in both adults and children [35]. The WADA test remains a valid alternative in places where functional MRI is not available but should not be used as a standard due to its invasiveness and limited informative value [36].

Specification of the pediatric “awake situation” and age limitations

Regarding the reviewed literature, ABS is safe, feasible, and well tolerated in children, even in the youngest reported with

an age of 8 years [19]. Nevertheless, the use of awake protocols in pediatric brain surgery remains limited due to assumed increased psychological fragility and vulnerability. Moreover, the pediatric population presents specific challenges related to cooperation, full understanding, and managing concomitant anxiety [21]. These factors become more relevant with decreasing age of the children and are translated in a cutoff limit for providing ABS to younger age groups [37]. In 1954, Pasquet noted that “uncooperative adults and children under 10 years” will not tolerate the application of local anesthesia, scalp incision, and craniotomy [38]. Contrarily, Klimek et al. demonstrated in their case report that an awake craniotomy is feasible and can be performed safely even in very young patients, and it seems unacceptable to uphold an age restriction [18]. An appropriate way to address this controversy is to identify the individual level of development and the correlated suitability of the child for this specific type of surgery by concise psychological and neuropsychological assessments. Notably, performing ABS in adolescents can be easily assimilated to awake procedures in adults. However, the psychological condition, temperament, and responsiveness of the individual patient determine the final perception of awake procedures in every age group [5, 39, 40]. Thus, individual psychological assessment and preparation of each patient undergoing ABS should be mandatory, adapted to the individual patients' age, temperament, and need in both groups, adults and children [41]. In addition, several studies confirmed that the extent and the quality of pre-operative psychological preparation and intra-operative support have a relevant impact on the psychological experience. Furthermore, they correlate with neuropsychological outcome [13, 15, 42]. Therefore, attempts should be made to establish eligibility criteria for the pediatric age group and to increase overall psychological support by qualified psychologists.

State-of-the-art

This review reflects the distinct results and specialty-related experiences of ABS in children. Besides reported clinical and psychological outcomes, it offers an overview of different diagnostic and preparative algorithms of the patients. In addition, variations of the intra-operative setup were documented. Although most of the studies report equally beneficial neurological results, the management of awake procedures varies and might at some point, especially from a psychological perspective, have an impact on the overall outcome and perception of the patient. Moreover, one could hypothesize that optimization, i.e., standardization of some management aspects, such as pre-operative imaging, neuropsychological preparation, support, and follow-up, can enhance the quality of eligibility assessment for patients being considered for ABS. Consecutively, this as a part of a

positive feedback loop would in turn increase the numbers of patient being offered that type of procedure. Having considered most aspects of ABS in children within this review, we derive from the reported results and experiences the following state-of-the-art recommendation:

- Pre-operative imaging should include functional MRI (fMRI) warranting precise assessment of the dominant hemisphere, localization of speech and motor function.
- Beneficial intra-operative technical support besides electrocortical stimulation may comprise neuronavigation for optimal lesion access as well as neuromonitoring for optimal morphological neuroprotection.
- Psychological/neuropsychological evaluation and preparation is mandatory for pre-operative eligibility assessment and final eligibility decision.
- Psychological/neuropsychological support should be offered during the operative procedure by the familiar professional, who provided the initial evaluation and preparation.
- Psychological/neuropsychological follow-up in the direct and long-term post-operative phase at 3, 6, and 12 months is advocated.
- Additional psychological/neuropsychological means or techniques may be applied adapted to the patient's age and need.

Following these recommendations and establishing the therefore required recourses are considered highly beneficial in the context of successful ABS in children. However, precise protocols on psychological/neuropsychological eligibility criteria that represent an important tool in the complex multi-disciplinary preparation of children for ABS remain pending.

Conclusion

This review confirms safety and feasibility, as well as reliable tolerability of ABS in selected children from a neurological and neuropsychological point of view; however, guidelines for its standardized implementation in this patient group are pending. Guidelines may integrate precise criteria of eligibility, psychological preparation, and support in an interdisciplinary approach in order to offer routinely ABS to children.

Compliance with ethical standards

Conflict of interest The authors declare that they have no financial or other conflicts of interest in relation to this review and its related research.

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