REVIEW ARTICLE

The impact of imposed delay in elective pediatric neurosurgery: an informed hierarchy of need in the time of mass casualty crisis

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Abstract
SARS-CoV-2 COVID-19, coronavirus, has created unique challenges for the medical community after national guidelines called for the cancellation of all elective surgery. While there are clear cases of elective surgery (benign cranial cosmetic defect) and emergency surgery (hemorrhage, fracture, trauma, etc.), there is an unchartered middle ground in pediatric neurosurgery. Children, unlike adults, have dynamic anatomy and are still developing neural networks. Delaying seemingly elective surgery can affect a child's already vulnerable health state by further impacting their neurocognitive development, neurologic functioning, and potential long-term health states. The purpose of this paper is to demonstrate that "elective" pediatric neurosurgery should be risk-stratified, and multi-institutional informed guidelines established.

Keywords SARS-CoV-2 COVID-19 · COVID-19 · Coronavirus · Craniosynostosis · Brachial plexus · Pediatric neurosurgery

Introduction

The COVID-19 pandemic has created unique challenges for pediatric neurosurgeons. Elective procedures have been postponed at virtually all major pediatric neurosurgery centers. While there has been some centralized effort in adult surgery to standardize and stratify low vs. high acuity [1], this has not yet occurred for pediatric neurosurgery. Given these new restrictions, many fields of medicine have made some general recommendations including head and neck surgery [2], anesthesia [3], cardiac electrophysiology [4], and colorectal surgery [5]. While some recommendations apply to neurosurgery, particularly endoscopic sinonasal and skull base recommendations [2], no manuscripts exist to systematically stratify risk associated with delay in common pediatric neurosurgical procedures.

The purpose of this paper is to outline the risks associated with delaying elective pediatric neurosurgery. Urgent cases that present an immediate threat to the patient's life or neurologic well-being (e.g., shunt malfunction, acute hematoma evacuation, tumor with hydrocephalus, empyema, spinal cord compression) are straightforward and undergo prompt surgical intervention. Elective surgery is readily defined as cases that offer a negligible or minimal threat of harm to the patient if surgery is delayed for several months. Examples might include skull dermoids/epidermoids, prophylactic spinal lipoma untethering operations, and some craniofacial procedures. These are similarly less challenging in the current environment. However, there are a large number of procedures which are less straightforward in which lack of prompt surgery, while not emergent, may result in neurologic harm to the patient. Delaying all "elective" surgeries in this population poses health-related risks, and a review of best available evidence on harm imposed by delaying these operations is warranted.

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Methods

The authors have identified a sample of pediatric neurosurgery procedures that are neither clearly emergent nor purely elective. Cases considered for review include the following diagnoses/scenarios:

1. Tumor recurrence without hydrocephalus
2. Chiari I malformation
3. Medically resistant epilepsy
4. Craniosynostosis—single suture and syndromic multi-suture synostosis
5. Tethered spinal cord
6. Brachial plexus
7. Moyamoya disease

A PubMed-based literature survey was conducted for manuscripts that addressed morbidity arising from delay in intervention for these diagnoses. Manuscripts were prioritized on the basis of relevance of study design and evidence quality and were excluded for the following reasons: opinion paper, review paper, single case report, lack of outcomes results, or pertaining to the adult population. Papers that presented outcomes from delayed surgery were included in this review.

1. Tumor recurrence without hydrocephalus or symptoms of mass effect (i.e., purely radiographic recurrence):

    i. Issues/threats with surgical delay:

        (a) Sudden decline from hemorrhage into tumor or acute development of hydrocephalus
        (b) Risks of dissemination or de-differentiation into higher grade lesion.

Supporting evidence Low-grade neoplasms characteristically show slow, linear growth with a minimal risk of rapid decline from mass effect [6]. For pilocytic astrocytomas, the greatest risk is likely the development of a cystic component that may show focal accelerated growth [7]. Other lesions such as craniopharyngiomas show highly variable growth patterns and often have a cystic component that may expand more rapidly to cause mass effect or obstruction [8]. Another important consideration in predicting potential risk for focal mass effect is the degree of surrounding edema elicited by the tumor. This risk also correlates with tumor histology [9]. Low-grade tumors such as pilocytic astrocytomas, glioneuronal tumors (DNT, ganglioglioma, etc.) and grade I gliomas typically offer a low risk for acutely developing edema [10]. High-grade pediatric lesions such as PNTs, embryonal tumors, choroid plexus carcinomas, or high-grade gliomas (e.g., glioblastoma multiforme) harbor substantially greater risk for edema and secondary rapid increase in mass effect [10].

Similarly, the incidence of hemorrhage into a tumor recurrence is predominantly determined by histologic diagnosis [11]. The pediatric brain tumors with the highest risk for hemorrhage include high-grade embryonal neoplasms of infancy [12], glioblastoma [13], and mixed malignant germ cell tumors [14]. As such, the prior histology of a recurrent lesion is the principle determinant of the acute risk for a sudden decline from hemorrhage or sudden edema. For example, Donofrio et al. [15] noted thin-walled, small, and closely packed vascularization in pediatric patients with cerebellar hemorrhage from pilocytic astrocytomas 10]. White et al. [16] characterized three distinct histological subtypes which correlated with hemorrhagic events in pilocytic astrocytomas [16]. Specifically, thick-walled hyalinized vessels with glomeruloid structures of vascular endothelial hyperplasia with ectatic vessels serve as a nidus for bleeds [16]. Multiple studies in the literature outline the relationship between histologic features and intratumor hemorrhage [15, 17–20]. Pagano et al. [21] describe recurrent hemorrhage of pilocytic astrocytomas and stressed the importance of VEGF for aberrant neovascularization and hyperpermeability [21]. Immunohistochemistry is now being better understood through genetic markers. As described by Phoenix et al. [41], medulloblastoma genotype highly dictates the vascular environment and hemorrhagic tendencies of tumors [22]. Most recently, Ishi et al. demonstrated the association of FGFR1 mutation with hemorrhagic events in low-grade pediatric gliomas [23].

2. Chiari malformation with syrinx

    i. Issues/threats with surgical delay:

        (a) Neurologic decline in upper extremities from syrinx
        (b) Dysesthetic pain from syrinx.

Supporting evidence Chiari I malformation has a range of clinical presentations from headaches to brainstem-related symptoms [24]. When patients are asymptomatic, the clinical course is benign overall [25, 26]. However, neurologic deficits arising secondary to syringomyelia may not be reversible with surgery. A recent practice preference survey by Rocque et al. [27] of the membership of the American Society of Pediatric Neurosurgery (ASPN) demonstrated a strong preference for using presence of a syrinx regardless of symptoms in the setting of Chiari I malformation as a threshold for surgery [27]. Most surgical series have reported a 60–85% incidence of syrinx with CIM but larger radiographic series show that only 10–15% of patients with a C1M have a syrinx [28, 29]. This

suggests that patients with syrinxes are selected in surgical series.

Several principles emerge that are helpful in approaching the dilemma of acceptable delay challenge for an asymptomatic patient with a C1M-related syrinx:

(1) The onset of neurologic symptoms from a C1M syrinx is usually insidious and gradual but can rarely be acute [30]. Only a limited number of papers address acute decline from C1M related syringomyelia [28, 31–34]. Massimmi [35] and colleagues identified 3 patients in their center experience and then identified 38 more patients from the literature that showed acute clinical decline [35]. They concluded in 2012 that only 41 of such patients had ever been identified and concluded that sudden presentation is extremely rare [35]. However, morbidity (irreversible motor 37%, 29% respiratory failure) and mortality (20%; 14.5% cardiac arrest) were severe when it did occur [35].

Almotairi and colleagues [36] observed 3 patients to acutely decline in a cohort of 65 (3/65 = 4.6%) adult patients from Sweden who were followed and treated for C1M-related syrinx [36]. In this series, the patients that declined acutely demonstrated longer and wider syrinxes that extended more rostrally (above C1) than the larger group who demonstrated no acute decline [36]. The extent of tonsillar herniation did not correlate [36].

(2) The response time of a syrinx to operative decompression is unknown and appears gradual. Wetjen and Oldfield [37] studied 29 patients who underwent posterior fossa decompression for C1M and found a median time of 3.6 months (95%CI = 3.0–6.5 months) [37]. Experienced Chiari surgeons typically advocate MRI imaging follow-up in 6–12 months.

(3) Surgical decompression has a consistently good but variable impact on syrinx. Tubbs et al. [29] found that only 4 out of 285 patients with syrinx demonstrated progression after posterior fossa decompression and cranioplasty [29]. Zhang and colleagues [38] demonstrated that 60% of patients who underwent posterior fossa decompression with duraplasty showed a reduction in size. Less is written or available on the time course of syrinx change and the common time point for observations is 6 months. A large meta-analysis by Durham and Fjeld-Olenec [39] that compared techniques of C1M decompression (decompression alone vs. decompression with duraplasty) demonstrated 56–87% syrinx resolution with operative decompression [39]. However, small numbers of syrinxes associated with Chiari I decrease in size over time without operative intervention and some syrinxes do not change after posterior fossa.

(4) Recovery of neurologic symptoms from a Chiari related syrinx is typically incomplete and permanent. The presence of a syrinx then represents a non-predictable risk factor for irreversible neurologic dysfunction from intrinsic chronic stress and injury to the spinal cord. Sudden decline is very rare but can occur especially from minor injury [28, 31–34].

Thus, it appears that there is a strong preference by experienced pediatric neurosurgeons to intervene for a syrinx associated with a C1M but the supporting evidence is incomplete and imperfect. The presence of the syrinx represents a threat to stress and low-grade chronic injury to the cord. It is very uncommon for acute symptoms to develop and the response to treatment usually occurs over months. Therefore, a modest delay appears of low risk but the presence of a syrinx appears to be a justifiable intervention in an environment of imposed surgical slow down due to rare but possible neurologic insult that is permanent.

3. Medically resistant epilepsy

By convention, only children with medically resistant epilepsy (MRE) are candidates for epilepsy surgery and most epilepsy surgery can be elective. There are however important criteria within the designation of MRE that help stratify patients with regard to the risk associated with operative delay. These include the risk for sudden death in epilepsy (SUDEP), the frequency and severity of status epilepticus (including status epilepticus in sleep or ESES), the overall seizure burden for the child, and the degree of medical resistance that the seizures demonstrate.

Issues/threats with surgical delay:

(a) Acute threat of catastrophic epilepsy: sudden death in epilepsy (SUDEP), non-reversible injury to the brain from status epilepticus, and ESES
(b) Sub-acute/chronic impact of uncontrolled seizures: the adverse effects to normal neurologic development from prolonged seizures
(c) Presence of a lesion (e.g., tumor, cavernomas)
(d) Palliative interventions: e.g., vagus nerve stimulator implantation.

Supporting evidence

Medical resistance/acute threats of MRE Defining and characterizing medical resistance (MRE): Candidacy for epilepsy surgery hinges upon defining medical resistance as a failure of 2 anti-epileptic medications at proper dose to confer control of seizures. Approximately one-third of patients with epilepsy will demonstrate MRE. These patients are candidates for surgical intervention and the overwhelming majority can be

evaluated and operated upon electively. However, an increased percentage of children have catastrophic epilepsy which is characterized by highly resistant and threatening generalized seizures. These often culminate in repeated episodes of status epilepticus and raise the risk for sudden death in epilepsy (SUDEP). Children with congenital or acquired structural anomalies of the brain such as hemimegalencephaly, holohemispheric dysplasias, hemispheric atrophy, and cystic encephalomalacia (often due to perinatal infarcts/ischemia) are more frequently found to have catastrophic epilepsy than those patients with more normal MRI findings. Syndromic epilepsies such as Lennox-Gastaut and Rasmussen's encephalitis are highly resistant and associated with progressively severe and difficult to control disease.

Similarly recurring episodes of status epilepticus, Epilepsia partialis continua, or electrical status epilepticus in sleep (ESES) threaten the child's safety and neurologic development. Children with malignant, threatening patterns such as these warrant an assertive, proactive approach to control and localization of their seizures. When accompanied by a structural change, these epilepsies are typically focal in onset and are amenable to surgical resection. Due to the acute risk and lack of other effective strategies, surgery for these cases is often considered urgent and is justifiable and appropriate to proceed to surgery in an environment in which elective cases are suspended.

Threat to cognition and neurocognitive development

There remains little doubt that uncontrolled epilepsy in children is injurious to the developing brain and adversely impacts normal neurocognitive development. The timing of epilepsy surgery is critical to achieve optimal long-term neurocognitive benefit. A retrospective study conducted by Jenny et al. [40] demonstrated higher seizure-free rate in infants (89.5%) vs. children (72.9%) [40]. Additionally, binary logistic regression demonstrated that younger children (less than 3 years of age) were 2.76 times more likely to achieve a seizure-free outcome compared with older children (4 to 17 years of age) [40]. Furthermore, developmental outcome as assessed by Loddenkemper et al. [41] using Bayley Scales of Infant Development demonstrated that younger age at time of epilepsy surgery was correlated with a higher improvement in the development quotient (correlation coefficient 0.72, $p < 0.001$) [41]. Finally, Pelliccia et al. [42] performed multivariate analysis using stepwise logistic regression to determine factors associated with seizure freedom and found a shorter duration of epilepsy to be significant (OR 0.92, 95% CI 0.89–0.94; $p < 0.001$) [42].

Lesional epilepsy

Lesional epilepsy represents a unique situation with regard to surgical decision-making. There are often 2 indications for intervention: (1) removal and histologic diagnosis of the lesion and (2) improved seizure control. The presence of a visible lesion in the region implicated by EEG and functional imaging to be epileptogenic markedly increases the likelihood of successful surgery. The most common etiologies for lesional epilepsies in children are ganglioneuronal tumors, cavernomas, and visible cortical dysplasias.

Gangliogliomas (GGs) and dysembryoplastic neuroepithelial tumors (DNETs) are low-grade brain tumors that commonly present with seizures. Seizure-freedom in this group of children is critical. As demonstrated by Englot et al. [43], seizure freedom is achieved with higher success in children less than or equal to 1 year of life compared with those greater than 1 year of age (OR 9.48; 95% CI, 2.26–39.66). Nolan et al. [44] performed a univariate chi-squared analysis to determine factors influencing favorable prognosis in children with DNTs and found shorter duration of epilepsy ($p = 0.01$) and younger age at surgery ($p = 0.04$) to be significant [44]. Finally, when evaluating cognitive outcomes, earlier surgery for tumor-related epilepsy is ideal. Ramantani et al. [45] conducted a retrospective review in children with glioneuronal tumors to determine factors that influenced cognitive outcomes. Lower full-scale IQ (FSIQ) and verbal IQ (VQ) were related to longer duration between diagnosis and surgery, when controlled for age at epilepsy onset (FSIQ $r = 20.537$, df = 22, $p = 0.007$; VIQ $r = 20.504$, df = 17, $p = 0.028$) [45].

The nearly uniform good outcomes from lesional resections for epilepsy along with a need for histopathologic diagnosis in many cases make a convincing case for proceeding to surgery even in the presence of initiatives to limit elective cases.

4. Craniosynostosis—single suture non-syndromic synostosis

(1) Issues/threats with surgical delay:

    ii. Candidacy for endoscopic techniques—typically endoscopic preferred less than 12 months

    iii. Capacity for bony defects to fill in declines with age

    iv. Thicker bone is more rigid and offers greater technical challenges with more bleeding, higher morbidity, and associated longer stay and higher cost.

(2) Supporting evidence:

    Endoscopic techniques in craniofacial surgery are being increasingly utilized due to good outcomes, lower morbidity, costs, blood loss, and equivalent or superior aesthetic outcomes. As demonstrated by Thompson et al. [46], endoscopic treatment utilizes less blood (26% vs. 81%, $p < 0.001$), coagulation products (3% vs. 16%, $p < 0.001$), anesthesia (168 vs. 248 min %, $p < 0.001$), surgical duration (70 vs. 130 min %, $p < 0.001$), days in ICU (0 vs. 2%, $p < 0.001$), and hospital LOS (2 vs. 4%, $p < 0.001$)

[46]. However, if a child is not seen within an appropriate timeframe, endoscopic craniosynostosis repair is no longer possible. While there remains debate about the superiority of endoscopic versus open repair, it is clear that in older children, only open repair can be performed.

As the skull matures, the capacity for spontaneous filling in of bony defects or gaps between bone grafts becomes reduced. Under the age of 18 months, the gaps between bone grafts are largely filled with fibrous tissue and islands of cartilage. The capacity to spontaneously fill and remodel bony defects dissipates with increasing age resulting in less satisfactory results in older children.

A retrospective study spanning 6 years, 44 states, and 8417 children under the age of 3 was conducted by Bruce et al. [47] to determine the optimal time to surgically repair craniosynostosis. Using the Healthcare Cost and Utilization Project Kids' inpatient database (KID), the overall complication rate was 8.6%: 6.6% for children aged 0 to 6 months, 10.3% for patients aged 7 to 12 months, and 13.9% in children aged 12 to 36 months [47]. Additionally, a multivariable logistic regression model to identify factors that increase perioperative surgical complication demonstrated age as a significant factor (OR = 2.53 at 3 years vs. < 1, 95% CI 1.67–3.82) [47]. Another study using the KID database showed delayed repair of craniosynostosis to be associated with longer length of stay (LOS) and increased cost [48]. In a sample of 3246 patients with an average age of 181 days, LOS directly impact mean charge and total cost [48]. When creating a regression model for factors that significantly impacted the length of stay, age was the most significant [48]. Older aged children had up to a three times greater odds of a longer LOS [48].

Syndromic multi-suture synostosis (e.g., Apert, Crouzon, Saethre-Chotzen, or Cloverleaf deformity): Multiple suture synostoses can give rise to brain constriction and elevated intra-cranial pressure that can be threatening to brain growth and optic nerve function. In the syndromic cases, the characteristic brachycephaly requires bi-frontal orbital advancement or distraction. The skull characteristically can be molded and reossification occurs readily until about the age of 2 years. After this, the bone is thicker, more brittle, and does not contour as readily. Consequently, there is likely limited harm in delaying syndromic cases inside of 2 years of age. Treatment of midface hypoplasia occurs in mid-childhood via distraction or LeFort midface advancement procedures.

5. Tethered spinal cord

The tethered cord syndrome (TCS) may arise from a variety of pathologic entities that share the capacity to fix the spinal cord to surrounding mesenchymal structures (e.g., bony spine or surrounding muscle and connective tissues) [49]. Symptoms usually consist of pain in the back, buttocks, and legs and variable but progressive loss of neurologic function in the legs and bladder [49]. Prevailing wisdom in pediatric neurosurgery is that once function is lost, it is typically not regained. Thus, the critical immediate distinction in tethered cord is between symptomatic and asymptomatic tethered cord. Intervention for asymptomatic tethered cord is largely prophylactic and is variably controversial depending on the underlying tethering lesion. For example, split cord malformations have a high incidence of inducing progressive neurologic decline unless repaired whereas the natural history of a low-lying spinal conus medullaris is less well established and there is significant controversy surrounding prophylactic untethering.

The fundamental question is the likelihood that delay in surgery may impart a decline in neurological function. Koyangi et al. [50] retrospectively described the efficacy of surgery given the natural history of tethered cord syndrome. Post-operatively, 7/8 (88%) asymptomatic patients remained this way, 6/26 (23%) improved, and 15/26 (58%) patients were unchanged [50]. Hoffman et al. [51] describe a similar relationship in a cohort of 97 pediatric patients. Fifty-six patients presented before the age of 6 months, and 35 of these patients were neurologically intact [51]. However, of the 41 patients presenting after the age of 6 months, only 12 patients were neurologically intact [51]. Surgery should be performed prior to the onset of neurologic deficits. As demonstrated by Kanev et al. [52] in a cohort of 42 patients presenting with neurologic deficit, 0/42 (0%) of patients regained bladder or bowel function post-operatively [52]. A logarithmic model developed by Kanev et al. using data from two series [51, 52] demonstrates that all patients would develop neurological deficits over time by 12 years of age [53]. While these studies do not provide definitive evidence of a danger with delay, they do suggest that prevention of deficit or worsening of deficits might be more successful with earlier surgery.

6. Obstetrical brachial plexus injury

Prompt neurosurgical evaluation is necessary to determine the level of the lesion and distribution of neurological injury [54]. While the most common presentation is that of an upper plexus injury (Erb's palsy) with damage occurring to the C5 and C6 roots [54], the most serious lesion is a total plexus lesion, which involves C5, C6, C7, and C8, with or without T1 [54]. The patient will present with a flail limb and possibly Horner's syndrome [54]. Prevailing opinion among surgeons from multiple disciplines is that these children require urgent exploration of the brachial plexus with appropriate nerve grafts and transfers [54].

For patients with an Erb's palsy, upper plexus, and pattern of lesion, there are multiple competing studies of various

quality regarding the ideal time of surgery [55–57]. A recent multicenter study [58] evaluated microsurgical outcomes in children who underwent plexus reconstruction before versus after 6 months of age. In the multivariable model, accounting for Horner syndrome and baseline Toronto score, there was no statistical difference in outcome between the early and late surgery (AMS score difference = 0.6, 95% CI = − 8.0 to 9.3, $p = 0.88$) [58].

In sharp contrast, total obstetric brachial plexus palsy injury requires more prompt surgical treatment and should ideally be performed around 3 months of age [59]. In a cohort of 35 patients with total obstetric brachial palsy injury, younger age at the time of surgery correlated with better functional recovery ($r = − 0.356$, $p = 0.049$), particularly with finger and thumb flexion [59].

Discussion

The onset of COVID-19 and the national guidance to delay elective surgery has changed the paradigms of operative pediatric neurosurgical practice. The need for social distancing and preservation, or limited availability, of personal protective equipment has resulted in widespread curtailment of elective operative procedures. During this time, it is essential to establish an informed hierarchy of need for pediatric neurosurgical cases. Many pediatric neurosurgery cases are urgent and must proceed. Examples include shunt obstructions, infections, post-traumatic hematomas, and myelomeningocele closures. Other cases are clearly elective and results are not likely impacted by limited delays. However, there exist a significant number of pediatric neurosurgical cases for which the impact of time delay in intervention is unknown. Some cases appear elective but review of published experience demonstrates that poorer outcomes or higher risk accompanies delay. An informed hierarchy of need incorporates the potential increase into adverse outcomes associated with delay as well as the imminent threat to the patient in the short term. The cases selected for this report are not comprehensive but are representative of a substantial component of elective pediatric neurosurgical practice. Within these cases, there are multiple examples of how a delay in performing surgery during an optimal eligibility window is associated with more adverse effects over the life span.

Additional factors that should be considered include the potential for exposure of risk to the operative team. Exposure risks not only center on airway control and intubation but also extend to risks associated with aerosolized particles including blood, CSF, and bone. Cases involving invasion into the airways and bony sinuses also carry elevated risks. Examples would include anterior skull base procedures, craniofacial procedures, and evacuation of empyemas that arise from erosion through bony sinuses.

Presurgical COVID19 screening should be implemented in areas where there is no current shortage of testing for symptomatic patients. If limited testing is available, cases in which exposure is gained endonasally should require preoperative COVID19 screening.

Ultimately, ideal timing should be explored for all pediatric neurosurgery. However, an effort that exhaustive is outside the scope of this manuscript's purpose of creating awareness on delay of common pediatric neurosurgical procedures. For the sake of completeness, some basic recommendations can be made regarding the procedures listed. For example, craniosynostosis repair should not exceed 4 months to prevent open surgery. Total obstetrical brachial plexus repair should be performed by 3 months of age to prevent neurologic deficit. Additionally, asymptomatic tethered cord and Chiari I malformation with syrinx should not be postponed longer than 6 months as the purpose of surgery is symptom prophylaxis. Lesional epilepsy represents a more complex disease process and a case-by-case evaluation is necessary depending on seizure burden, medication use, and concurrent tumor. As the referenced literature demonstrates, there are clear transition points in childhood (1 year of age and 3 years of age) that represent important checkpoints for intervention.

In sum, there are multiple levels of consideration when properly assessing the timing of surgery. Imminent danger to the patient is foremost but the potential for adverse outcomes from missing an optimal time window of eligibility should also be considered. This review has demonstrated multiple examples of common pediatric neurosurgical procedures where such phenomena are observed. Finally, considerations of operative team exposure and resource utilization need to be considered.

Conclusion

Proper evaluation of the timing of a pediatric neurosurgery case must extend beyond the period of an imminent threat to the patient. Evaluation of a representative sample of pediatric neurosurgical cases demonstrates how adverse outcomes arise consistently when important optimum time windows of candidacy are missed. In addition, exposure risk and resource consumption in an era of scarcity must be considered to attain the best overall decision regarding the timing of pediatric neurosurgical intervention.

Compliance with ethical standards

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