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Childhood Hemorrhagic Stroke: An Important but Understudied Problem

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Abstract

Hemorrhagic stroke in children occurs more frequently than is commonly appreciated. There are important differences in the factors associated with hemorrhagic stroke in children when compared with adults. These differences likely play a role in the different outcomes, which tend to worsen with age. In this review, we describe the estimated frequency, clinical presentation, acute management of hemorrhagic stroke, and an overview of rehabilitation techniques. We identify key topics for future basic and clinical research. Findings from future studies will help improve our ability to optimize treatment for and long-term rehabilitation of these patients.

Keywords

Hemorrhagic stroke; pediatric; intracerebral hemorrhage; subarachnoid hemorrhage; treatment; children

Introduction

Several factors have fueled interest in pediatric stroke over the past 20 years: the sustained efforts of a core group of investigators, imaging technology that simplifies detection of ischemic stroke,^{1,2} and the rise of multicenter consortiums that support data gathering. Most studies have focused on ischemic stroke; hemorrhagic stroke has achieved far less notice. As a consequence, we know more about associated factors^{1,5} and treatment patterns^{3,4} with ischemic stroke, but much less about hemorrhagic stroke. Most of our knowledge regarding hemorrhagic stroke comes from a small number of case series;^{5–10} large registry-based or cohort studies simply don't exist.

In this review, we examine evidence that suggests childhood intracerebral and subarachnoid hemorrhages are more common than previously believed. We will briefly address clinical presentation, acute general management, and some specific aspects of rehabilitation. Lastly, areas that are ripe for clinical and basic research will be noted. The term hemorrhagic stroke will refer to subarachnoid or intracerebral hemorrhage; intracerebral hemorrhages may involve the parenchyma or the ventricles. (Figures 1 and 2) Intraventricular hemorrhages in premature infants, subdural and epidural hemorrhages, traumatic hemorrhages, and hemorrhagic conversion of ischemic infarcts will not be discussed.

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Frequency of Childhood Hemorrhagic Stroke

A small number of studies have examined the frequency of childhood hemorrhagic stroke in well-defined populations. A retrospective study of Rochester, Minnesota, from 1965 to 1974 found hemorrhagic stroke accounted for 31 of 69 cases (45%).¹¹ A retrospective study of greater Cincinnati, Ohio, from 1988 through 1989 found hemorrhagic stroke accounted for 9 of 16 cases (55%).¹² A prospective study of Dijon, France, from 1985 through 1993 found 11 hemorrhagic strokes out of 28 cases (39%).¹³

These earlier studies reported the incidence of hemorrhagic stroke in local regions, but not at state/provincial or national levels. Population-based studies at those levels do not exist. Administrative databases are one means that can be used to estimate the frequency of strokes at the state or national level. Administrative data should be considered cautiously since the databases typically were not developed for epidemiological study and the accuracy of the diagnoses depend upon the practices of the participating institutional medical record departments. The assumption when using these datasets is that because they report such large numbers of cases, one can estimate the frequency of diseases that do not occur commonly. A study of a California state database from 1991 through 2000 examined cases of first-time discharges where stroke was listed in any diagnostic position. That study identified 2278 childhood cases, of which hemorrhagic stroke accounted for 49% (33% were intracerebral and 16% were subarachnoid).¹⁴ We analyzed a US dataset that covered hospital discharges for children in 2003. There were 2224 cases with stroke as the first discharge diagnosis and excluding trauma. Of that total, 994 (45%) were coded for hemorrhagic stroke, of which 514 were intracerebral hemorrhage (23%) and 480 were subarachnoid hemorrhage (22%).¹⁵

More recently, we analyzed an administrative database of 24 US children's hospitals for cases where the primary discharge diagnosis was stroke and trauma codes were excluded. For the years 2003 through 2009, there were 1667 individuals with a primary diagnosis of stroke. Of those, 704 (42%) had a primary hemorrhagic stroke diagnosis. Lastly, a retrospective analysis was performed of a large cohort in northern California covered by a health maintenance organization. The investigators reviewed the records to verify the clinical and radiological diagnosis of stroke. They found 116 non-traumatic hemorrhagic strokes from January 1993 through December 2003¹⁶ and 97 ischemic strokes from January 2003 through December 2004.¹⁷ Although the years examined are not exactly comparable, if one pools these results, hemorrhagic stroke accounts for 54% of that total.

Collectively, these studies provide consistent estimates that hemorrhagic stroke accounts for between 39% to 54% of all childhood stroke, which indicates that intracerebral and subarachnoid hemorrhage are important causes of childhood stroke. In contrast, hemorrhagic stroke in adults accounts for a far smaller proportion of stroke. In adults intracerebral hemorrhage accounts for 6.5% to 13% of all strokes.^{18–20} In these same studies, subarachnoid hemorrhage accounts for 1% to 6% of all strokes. Hemorrhagic stroke accounts for 7.5% to 19% of adult strokes, a lower proportion than in children. One may conclude that primary hemorrhage is an important component of childhood stroke and that hemorrhagic stroke in children is a greater source of mortality and morbidity than in adults.

Factors Associated with Childhood Hemorrhagic Stroke

No studies have systematically examined potential risk factors for hemorrhagic stroke in children. The best available information comes from case series or the cohort studies reported above. Individually, the series are limited by small numbers of subjects, different inclusion and exclusion criteria, and no uniform evaluation for risk factors. However, if one pools the results of multiple studies it is possible to develop a rough estimate of factors

associated with hemorrhagic stroke. Reports from neurosurgical centers may be skewed toward surgical cases, but several reports analyzed hemorrhagic stroke associated with medical as well as surgical causes (Table 1).

As demonstrated in the accompanying table, intracranial vascular anomalies (arteriovenous malformations, aneurysms, cavernous malformations) were associated with 48% of cases. Brain tumors were associated with 9% of cases and in 19% of cases no cause for the hemorrhage could be identified. Of the 23% associated with medical causes, a range of factors were evident (Table 2).

If one examines case series that reported medical causes in detail, hemostatic defects, either acquired or genetic, occurred in 9%, and thrombocytopenia in 6%. Infection (either central nervous system or systemic) or systemic illness was present in 9% of the cases. Four percent were associated with systemic malignancies and only 2% were thought related to hypertension. What is difficult to appreciate from this type of table is the overlap that can occur between conditions. For example, thrombocytopenia may occur in a systemic infection or due to cancer chemotherapy; an acquired coagulopathy may occur with septic shock or severe organ failure. Missing from this analysis is neonatal hemorrhagic disease occurring where newborns do not routinely receive vitamin K.²¹

This pattern of associated factors is very different from that in adults, in whom age, hypertension, smoking, cerebral amyloid angiopathy, oral anticoagulants, and chronic alcohol use are risk factors for intracerebral hemorrhage.^{22,23} The pattern in children is also quite different from the risk factor profile for subarachnoid hemorrhage in adults in whom age, gender, ethnicity, smoking, alcohol use, hypertension, and sympathomimetic agents are risk factors.^{24–27} In brief, hemorrhagic stroke in children tends to be associated with intracranial vascular anomalies or medical disorders, with a significant minority of children having no identifiable factor.

Clinical Presentation

Hemorrhagic strokes in young children may have very nonspecific clinical features, so that a high level of suspicion may be needed to reach a prompt diagnosis. In older children the clinical features usually point more quickly to an intracranial problem. We reviewed the records of 85 children at a single institution who had radiology-confirmed intracranial hemorrhages; 14 had subdural hemorrhages (Table 3).⁷

Of 34 children who were younger than age 6, the most frequent presenting signs were nonspecific, such as altered mental status or convulsions. Focal neurological signs were not common and, as might be expected, young children did not report headache. In children 6 years or older, most were able to report headache and a substantial proportion had focal neurological signs (Table 4).

While no child presented with all listed clinical signs or symptoms, the consistent pattern in the presentations was the abrupt onset of several of these clinical signs followed by progressive neurological deterioration.

General Treatment Measures

The surgical management of intracerebral and subarachnoid hemorrhages is too extensive to describe in detail here, but basic aspects of medical management will be reviewed briefly. Of 3 published treatment guidelines that dealt with childhood stroke,^{28–30} only one dealt with hemorrhagic stroke.³⁰ Many of the steps that follow were adapted from the single published guideline for children and supplemented by guidelines for adult hemorrhagic

stroke.^{31,32} Whether these measures actually improve outcomes has not been rigorously examined in children. Whether adult-based recommendations are appropriate for children will need to be confirmed in future studies.

A patient with an acute hemorrhagic stroke should be monitored in an intensive care unit staffed by physicians and nurses with neuroscience expertise. While an awake patient may be monitored noninvasively, patients who progress to or present with significant alteration of consciousness should have intracranial pressure monitoring, and cerebral perfusion pressure should be maintained between 50 mm Hg to 70 mm Hg. Any further clinical deterioration should be promptly evaluated with a CT scan to look for acute hydrocephalus, extension of an intracerebral hematoma, herniation, or vasospasm in a patient with subarachnoid hemorrhage. Protective reflexes may be impaired so that the stability of the airway must be ensured. If there is loss of respiratory drive, loss of protective airway reflexes, or cardiorespiratory instability, the patient should be intubated and mechanically ventilated. Intravenous access is important to maintain circulatory homeostasis and to prevent dehydration. Hypotonic fluids may contribute to cerebral edema so they should be avoided in favor of with normal saline fluids. As stroke may impair swallowing, nothing should be given by mouth until the risk of aspiration can be adequately assessed in the alert patient.

There is no present evidence that hypothermia improves outcome after intracerebral hemorrhage. Studies in adults have shown an association between hyperthermia and poorer outcome in ischemic stroke,^{33,34} but there has been little investigation of this association in hemorrhagic stroke. Animal studies do not show a clear link between hyper- or hypothermia and outcome after experimental intracerebral hemorrhage.^{35–37} Two small studies in adults^{38,39} suggested a link between hyperthermia and poorer outcome of hemorrhagic stroke, but one study used historical controls and the other found that fever was confounded by intraventricular hemorrhage. Despite the lack of evidence, treating hyperthermia to achieve normal temperature seems reasonable.

Clinically significant hypertension occurs far less frequently in children with hemorrhagic stroke than in adults. Upon presentation to an emergency department, 27% of adult patients with intracerebral hemorrhage have blood pressures greater than 160/100 mm Hg.⁴⁰ In the 4-case series noted above, hypertension was considered to be the cause of intracranial hemorrhage in only 3 of 195 children. Therefore, many of the adult guidelines do not apply to children. When blood pressures are substantially higher than age-specific norms treatment is reasonable, but overly rapid reduction of blood pressure may compromise cerebral perfusion. The prudent recommendation is that treatment of elevated blood pressure should be gradual and should avoid hypotension or compromise of cerebral perfusion pressure.

Severe increased intracranial pressure or compartmental herniation can expand the zone of injury and lead to further neurologic deterioration. One should suspect severe edema or mass effect with increased intracranial pressure if there is deterioration in the level of consciousness, the appearance of periodic breathing, or pupillary asymmetry. If these clinical changes occur, repeat CT scan imaging may be necessary to distinguish the effects of increasing cerebral edema from rebleeding or rupture of hemorrhage into the ventricles.

Hyperosmotic treatment with mannitol can lower intracranial pressure, but the effect tends to decrease over time. Hypertonic saline (7.2% saline with hydroxyethyl starch; 10% or 23.4% saline) has been used in patients with increased intracranial pressure after traumatic brain injury. Hypertonic (10%) saline, was effective in reducing intracranial pressure when mannitol was no longer effective in a small series of ischemic stroke patients.⁴¹ Three small trials found that hypertonic saline was slightly more effective than mannitol in lowering

intracranial pressure in patients with stroke or brain injury.^{42–44} Despite initial positive reports favoring hypertonic saline over mannitol, neurointensivists remain split between the use of mannitol versus hypertonic saline.⁴⁵

Vasogenic edema sometimes occurs after a cerebral hemorrhage. Corticosteroids are not helpful with cytotoxic edema, but individuals with vasogenic edema may benefit from corticosteroids.

Management Specific for Intracerebral Hemorrhage

If a patient has a known severe hemostatic factor deficiency, then that factor should be replaced. Patients who have severe thrombocytopenia, if not due to an immunological disorder, should be treated with platelet transfusions. Patients treated with warfarin who develop intracranial hemorrhage can be treated with intravenous vitamin K, fresh frozen plasma, or prothrombin complex concentrate to increase levels of coagulation factors. Bleeding during anticoagulation with unfractionated heparin can be treated with protamine sulfate, but protamine only reverses the effect of low-molecular weight heparin by 70%. All these measures pose a risk of thromboembolism. Therefore, certain circumstances (for example, a small, stable intracerebral hemorrhage in the cerebral hemisphere) may warrant clinical judgment rather than treatment. The role of recombinant factor VIIa is not clear. The recombinant factor reduced hematoma growth in a phase 3 trial in adults but did not improve outcome, and the highest dose was associated with increased numbers of thromboembolic events.^{46,47}

Clinical seizures occur in a substantial number of children, with percentages ranging from 26% to 37%.^{6,8,10} This frequency is probably higher than that in adults, although the percentage of adults with clinical seizures varied widely in recent reports (1.7% to 31%).^{48–51} Patients with large or expanding hemorrhages or hemorrhages located in the cerebral cortex are at higher risk of seizures (Figure 3).^{48–50}

The role of routine prophylaxis in the absence of clinical seizures is unclear, for one study in adults⁴⁹ found that those who received prophylactic anticonvulsants had a poorer outcome. Electrographic seizures are an additional concern; in one adult series 28% had electrographic seizures and in another series 18% were affected.^{48,52} The effect of electrographic seizures upon hemorrhagic stroke outcome is not clear⁴⁸ and the extent to which they should be treated is controversial, but given these uncertainties, it seems reasonable to pursue appropriate monitoring and treatment if circumstances suggest the occurrence of nonconvulsive seizures.

There is little data to support routine craniotomy in adults with supratentorial intracerebral hemorrhage,^{53,54} but there may be a role in children for decompressive hemicraniectomy if there is severe hemispheric edema. Early hemicraniectomy improves survival and functional outcome in adults with malignant middle cerebral artery syndrome.^{55–57} Two small series in children reported that hemicraniectomy was lifesaving in massive cerebral ischemic infarction,^{58,59} but there has been little experience in childhood hemorrhagic stroke.⁶⁰ With severe supratentorial hemorrhage and edema, surgical decompression may limit hypoperfusion or herniation injury. In that case, decompressive hemicraniectomy may be an option in selected patients.

In the posterior fossa the case for early decompression is clearer. A patient who is stable and who has a small posterior fossa hemorrhage may be observed closely without intervention. Signs of hydrocephalus or brainstem compression due to a cerebellar hemorrhage should lead to decompression, which can be life-saving. Ventriculostomy should be considered to

alleviate a progressing hydrocephalus, but careful monitoring is needed because upward herniation of the cerebellum and brainstem can occur.

Management Specific for Subarachnoid Hemorrhage

Many of the general principles stated above apply to the management of subarachnoid hemorrhage. These patients are at risk for hyponatremia (10% to 30%) so one should avoid hypotonic fluids and hyponatremia should be corrected.³² Fluid restriction should be avoided because it may lead to decreased cerebral perfusion.

Since fever can increase the cerebral metabolic rate, it is reasonable to identify the cause, and treat fever. A small case-control study in adults found that active cooling was associated with a lower risk of poor outcome compared with routine fever control,⁶¹ but the significance of this finding is not clear since fever is associated with initial poor clinical grade and intraventricular hemorrhage in adults.⁶² There are no well-controlled studies that demonstrate blood pressure control reduces rebleeding,³² so efforts to control sustained severe hypertension should be gradual and should avoid impairing cerebral perfusion.

Seizures occur in 6% to 25% of adult patients who have subarachnoid hemorrhage;⁶³ those who present with a poor clinical grade or who have thick cisternal blood have a higher risk of seizures (Figure 4).^{64,65}

Patients who are obtunded may have nonconvulsive status epilepticus.⁶³ While there is concern that recurring convulsions may increase the risk of rebleeding, the value of routine anticonvulsant prophylaxis is uncertain. One re-analysis of 4 clinical trials⁶⁶ found that routine prophylaxis was used in 65% of patients, but use varied by country and center. That study found prophylactic antiepileptic medication prescription was associated with poorer outcomes.

There is little data regarding the occurrence of vasospasm in children, so evaluation and treatment recommendations are at best speculative. In a recent re-analysis of 4 clinical trials in adults, clinically symptomatic vasospasm occurred in 33% of subjects.⁶⁷ The risks of clinically significant vasospasm are higher in patients who have moderate to severe subarachnoid hemorrhage and who present with poorer clinical grades. Clinically significant vasospasm in adults typically begins 3 to 5 days after the initial bleed and develops as a gradual decline in neurologic function.³² A randomized clinical trial in adults showed that oral nimodipine reduced the frequency and severity of ischemic neurological deficits when given routinely after the onset of hemorrhage.⁶⁸ Accordingly, oral nimodipine should be considered as a prophylaxis in patients who have had moderate to severe subarachnoid hemorrhage, although there is little experience with nimodipine in children. If clinically symptomatic vasospasm has occurred, vasospasm may be treated with volume expansion, moderate systemic hypertension, and hemodilution to improve perfusion.³²

Evidence in adults indicates that elimination of the aneurysm should be performed as early as possible to decrease the risk of a recurrent hemorrhage.³² Rebleeding increases the risk of death or poor outcome to 70% to 80% in adults, so early intervention (hours to days) to occlude an aneurysm should be pursued if a patient is stable and likely to survive.³² One limitation to these management suggestions is that the rebleeding rate in children is not well-understood. In one cohort study, described below, no rebleeding was reported,⁶⁹ while in another case series 7 of 17 patients had rebleeding.⁷⁰ Depending upon the location, anatomy, number of aneurysms, and the age of the patient, one might use combined endovascular and microsurgical approaches to manage a given case.^{71,72}

Chronic Management of Hemorrhagic Stroke

A recent population-based cohort study examined factors for recurring hemorrhagic strokes in children.¹⁶ Over a 10-year period, 116 children had a nontraumatic hemorrhagic stroke. Eleven children had a recurring hemorrhagic stroke occurring between 7 days to 5.7 years after the incident hemorrhage. The 5-year cumulative recurrence rate was 10%. Most recurred within 6 months after the initial hemorrhage. There were no recurrences in children with idiopathic hemorrhagic stroke. Children who had structural lesions, specifically arteriovenous malformations, cavernous malformations, or central nervous system tumors had a recurrence rate of 13%. Children who had underlying medical causes had a recurrence rate of 13%; their recurrences tended to occur within a week of the first hemorrhage. This cohort was re-analyzed to determine the proportion of children who had cerebral aneurysms as a cause of hemorrhage.⁶⁹ Seventy-five of the 116 children had vascular imaging and 15 of the 75 had a cerebral aneurysm. Of that 15, 12 had subarachnoid hemorrhage only, 2 had mixed intracerebral hemorrhage and subarachnoid hemorrhage, and 1 had pure intracerebral hemorrhage only. None of the patients with aneurysms had a recurring hemorrhage.

Given the recurrence risk of hemorrhage with intracranial vascular anomalies, they should be corrected when possible. Although the risk for aneurysm rebleeding is uncertain, the adult experience suggests that occlusion of the aneurysm at the earliest feasible opportunity is ideal. The child should be managed at a center staffed with neurosurgeons and vascular interventionalists who have experience in these fields.

Outcome of Hemorrhagic Stroke

Few studies have examined predictors of outcome in children, but 2 single-center studies^{6,73} have shown that when the ratio of intracerebral hemorrhage volume to brain volume is than 2% to 4%, outcomes are poorer. One study⁶ did not find an association between intraventricular hemorrhage and outcome. In our own unpublished work we assessed outcome (median time to follow-up was 5.1 years) in 19 of 59 children after intracerebral hemorrhage. We found that the initial Glasgow Coma Score, hemorrhage location, and ventricular involvement did not predict outcomes. The ratio of hemorrhage volume to brain volume positively correlated with increasing disability and poorer quality of life. Certain associated diagnoses correlated with poorer quality of life outcome. Together these findings suggest that adult predictors for outcome are not strong predictors of outcome in children intracerebral hemorrhage. One possibility is that the childhood studies are underpowered to exclude a type II error. The finding is not surprising, however, because the factors associated with hemorrhagic stroke are very different between children and adults.

Are outcomes in children better than in adults? Current studies provide a mixed picture. Studies that followed children for longer times and had broader inclusion criteria tended to reveal higher mortality rates. The studies in children are small in sample size, but if one pools those that note outcome (almost all deal with childhood intracerebral hemorrhage), several general points appear.^{6,7,9,74–77} About 38% of children have a good outcome with apparently little impairment, but most studies provided no cognitive function data. Another 29% have deficits that range from moderate to severe in magnitude. One third die from acute hemorrhage, recurring hemorrhage, or from an underlying disorder.

Two case series examined functional outcomes in more detail. One performed neuropsychological examinations of 31 survivors of hemorrhagic stroke. No cognitive deficits were found in 15 survivors, mild or diminished cognitive function were found in 8, and 7 had moderate to severe global cognitive deficits.⁷⁴ Another study of 26 patients with intracerebral hemorrhage found that half of the survivors had cognitive deficits and 38% had motor deficits.⁵ Together these studies suggest that hemorrhagic stroke in children has a

high rate of mortality and a substantial proportion of survivors have functional impairment. In comparison, adult subarachnoid hemorrhage is associated with fatality rates ranging from 20% to 45%^{78,79} and risk of dependency approaching 50% in survivors. In a recent meta-analysis,⁸⁰ the median fatality rate for adult intracerebral hemorrhage was 40%, with only 12% to 39% of survivors achieving independence. Given the available data, one can argue that survival and functional outcomes in children are modestly better than in adults.

Rehabilitation

Space limitations preclude a detailed discussion of stroke rehabilitation, and aspects of constraint therapies will be addressed elsewhere in this monograph. Nevertheless, some mention of rehabilitation is important, for it is where the clinician can have substantial impact. There is little information regarding rehabilitation that is specific to hemorrhagic stroke, but if stroke from hemorrhage is simply another form of acquired central nervous system injury, perhaps there is no difference in the rehabilitation of hemorrhagic versus ischemic stroke. This assumption needs to be tested, for there has been no comparison of outcomes between ischemic and hemorrhagic stroke. Furthermore, the contributing factors for the 2 types of stroke are very different.

The severity of a child's post-stroke deficit depends upon the size and location of the child's stroke, whether the child has one or multiple strokes, and any associated medical factors. Depending upon the severity of deficits children usually benefit from an initial multidisciplinary evaluation, with possible inpatient rehabilitation followed by outpatient therapy. Rehabilitation, adapted to the child's developmental level, should start as soon as the child can tolerate therapies to preserve mobility and strength, and then continue and adjusted as function evolves during recovery.

Constraint-Based Therapies

These therapies will be addressed in more detail elsewhere, but some brief notes will be made here. These approaches were developed from animal and clinical pilot studies in which the unaffected upper extremity was immobilized while the upper extremity affected by a stroke was intensively exercised and step-wise training of increasingly complex tasks occurred.⁸¹ A randomized clinical trial in adults with chronic stroke showed that constraint-induced movement therapy produced a significant improvement in motor function compared with routine standard of care.⁸² Subsequent studies showed that constraint-induced movement therapy was effective even when initiated 15 to 21 months after adult stroke,⁸³ and positive effects of constraint-induced movement therapy persist at least 2 years after the intervention.⁸⁴ Techniques for the arm have been adapted to involve the leg,⁸⁵ and constraint techniques have been applied to treat aphasia.⁸⁶

There has been considerable interest in constraint-based therapies for children with hemiplegic cerebral palsy and stroke. The evidence for efficacy has been based upon relatively few trials that involved small numbers of subjects, predominantly with congenital hemiplegia.⁸⁷⁻⁹¹

The extent of efficacy in children is controversial. There are reports of significant functional improvement for stroke and congenital hemiplegia.⁹¹⁻⁹³ These reports have been counterbalanced by a recent Cochrane review that recommended constraint therapies be considered experimental in children,⁹⁴ and a separate meta-analysis that only found small to moderate treatment effects for constraint-induced movement therapy in children with congenital hemiplegia.⁹⁵ Multicenter trials have been proposed to compare the efficacy of constraint-induced movement therapy with intensive rehabilitation or standard care,⁹⁶ or with traditional bimanual training.⁹⁷ A trial in which all subjects will receive botulinum

toxin for spasticity prior to randomization to constraint-induced movement therapy or traditional bimanual training also has been proposed.⁹⁸

Beyond the degree of efficacy there are uncertainties about the treatment of children. Regarding the intensity of treatment, Taub showed in a small trial that constraint-induced movement therapy for children with 6 hours of training for 3 weeks at 5 days a week had the same effect as 6 hours a day for 21 consecutive days.⁹¹ How young a child may be treated,^{93,99} the type of restraint,¹⁰⁰ the duration of treatment per session,^{89,101} and which children will tolerate constraint-induced movement therapy^{102,103} are all questions that have yet to be answered by pilot studies that are currently underway.

Residual Motor Deficits

Motor weakness is the most common immediate manifestation of childhood stroke, but weakness is gradually replaced by spasticity in most individuals who fail to recover completely. The degree to which spasticity impairs long-term function depends on its severity. Treatments include physical and occupational therapy, medications, and surgery. Physical therapy is the modality that is used most often, but there is surprisingly little objective evidence for its effectiveness. Light orthotic devices, such as an ankle-foot orthosis, wrist-hand splint, or a knee-foot-ankle orthosis, may be used to counteract increased tone to maintain a more functional posture and to assist with therapy. Occupational therapists can help the patient adapt the use of an impaired hand to perform activities of daily living.

Medication treatment of chronic spasticity is similar to the treatment used for children with cerebral palsy.¹⁰⁴ Diazepam and baclofen are the 2 oral medications used most often. With either drug, the basic principle is to start with a low initial dose, then gradually titrate upward based upon spasticity response and side effects. Diazepam is more often used in infants. Baclofen has been used in older children for many years and is generally tolerated well. Medication should complement ongoing physical and occupational therapy. The therapist can often help gauge the response to treatment. Locally injected botulinum toxin can reduce the severity of spasticity and dystonia. The effect lasts for a few months, so repeated injections are needed.

Children with congenital hemiplegia are treated with botulinum toxin combined with upper-limb training, constraint-induced movement therapy, hand-arm bimanual intensive training, and neurodevelopmental therapy. No modality appears to be superior, although in a meta-analysis, treatment effects were large for intramuscular botulinum toxin coupled with upper limb training, while the other 3 therapies had small to medium treatment effects.⁹⁵

Surgical options for severe medically refractory spasticity include an intrathecal pump for baclofen infusion. If that is not effective, selective dorsal rhizotomy may be considered in carefully chosen patients. The relative merits of intrathecal baclofen and selective rhizotomy are still debated, but rhizotomy should probably be done in a center with experienced personnel and age-appropriate ancillary services.

Dystonia can be a disabling sequel of stroke. Acute dystonia occurs in occasional children who have a basal ganglia infarction. Chronic dystonia is more likely to occur following a stroke in the basal ganglia and typically occurs in an extremity that was weak at onset of the stroke. The triad of dystonia, weakness, and spasticity often occur in the same extremity. Pharmacological treatment of stroke-related dystonia has been disappointing.

Dysphagia may occur after stroke, and before attempting to feed the patient the integrity of swallowing may need to be confirmed with the assistance of a speech therapist or

radiographically by a modified barium swallow study. If aspiration is present, interventions, including a feeding tube, may be necessary. If disruptions in swallowing persist, a gastrostomy may be needed.

Aphasia and Dysarthria

Aphasia can be difficult to distinguish from other cortical dysfunctions and from dysarthria. A speech therapist can provide valuable assistance in categorizing the nature of the child's speech disturbance. Children who have dysarthria from a hemispheric lesion often improve, but those who have dysarthria from a brainstem stroke may have persistent deficits. Many children who have acute aphasia improve to a degree. While no controlled trials prove the effectiveness of speech therapy in children after a stroke and it can be difficult to link a given child's improvement to the therapy, some children appear to benefit. Children with dysarthria seem to benefit more from speech therapy than those who have aphasia.

Cognition and Behavior

Recent studies indicate that a substantial proportion of children have residual cognitive, behavioral, and language deficits after strokes. With sophisticated cognitive testing, subtle deficits can be detected in children who formerly would have been thought to have recovered completely. Studies that examined cognitive function after childhood stroke generally found that overall cognition falls in the average range, but shifted toward the lower end of normal. This pattern has been best characterized in childhood ischemic stroke,¹⁰⁵ but small hemorrhagic stroke cases have similar findings.^{5,74} The impairment in cognitive function may be fairly selective,¹⁰⁵ so parents and teachers may miss a significant deficit when overall cognitive function is intact.

Various behavioral changes can occur after a stroke, again best characterized in ischemic stroke. Children with executive function impairment may have attention symptoms that mimic attention deficit disorder, and may be difficult to sort out.^{106,107} The frequency of depression in children after a stroke is not known, but seems to be common, at least in ischemic stroke.¹⁰⁸ Symptoms of depression can be difficult to distinguish from the chronic effects of the stroke, but problems with sleep, cognitive changes, and behavioral issues should alert the clinician to the possibility of depression. Size of the lesion and the extent of functional impairment are not reliable predictors of depression. There is debate about whether the location of the stroke correlates with the likelihood of post-stroke depression. A prior history of depression or a positive family history should increase the level of suspicion.

Epilepsy After Stroke

Seizures occur in 15% to 30% of children with acute hemorrhagic stroke, but there is little correlation between the occurrence of seizures acutely and the development of chronic epilepsy later. Long-term prophylactic antiepileptic agents are unnecessary given the relatively low percentage of children who develop epilepsy after a stroke. However, children who develop late-onset epilepsy will need appropriate antiepileptic medication. For medically refractory epilepsy or with underlying structural anomalies such as arteriovenous malformations, surgical resection may be appropriate.

Areas for Future Research

Given the gaps in knowledge about childhood hemorrhagic stroke, there are multiple opportunities for clinical and bench research. Clinical studies that can build upon existing work include: (1) further characterization of variables that can predict outcome; (2) determining whether decompressive hemicraniectomy has a role in managing severe intracranial hemorrhage; and (3) determining the scope of cognitive and behavior

impairments in survivors with hemorrhagic stroke and comparing the deficits that resemble those following ischemic stroke. Additional clinical studies might be considered despite the lack of positive results in adults because the mechanisms for hemorrhagic stroke are different between the 2 ages. Such studies include hypothermia in severe hemorrhagic stroke, recombinant factor VIIa, and intraventricular thrombolysis.

Hemorrhagic stroke has received far less attention than ischemic stroke in the basic science arena, and the work that has been performed has not examined the effects of hemorrhage in immature models. The existing models of subarachnoid hemorrhage and intracerebral hemorrhage have limitations,^{109–111} but can still provide insights into the mechanisms of injury. A recently reported model of injected supratentorial blood in the piglet¹¹² may provide novel insights that could be relevant to childhood intracerebral hemorrhage.

In summary, hemorrhagic stroke is a more frequent cause of childhood stroke than is generally appreciated. The associated factors are quite different than those that occur in adults, and that may explain in part why outcomes in children are modestly better than in adults. There are few guidelines for the acute management of hemorrhagic stroke and much has to be borrowed from adults. The validity of guidelines modified from adults should be validated with future study. There are opportunities for clinical and basic research, which may provide insights that can help improve our acute treatment and the long-term rehabilitation of our patients.

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Figure 1.
Computed tomographic brain scan (CT scan) showing an acute brainstem hemorrhage with acute hydrocephalus.

Figure 2.

CT scan showing acute subarachnoid hemorrhage. This scan also illustrates 2 key points about intracerebral aneurysms in children; they can be posterior and are frequently larger or more complex than in adults.

Figure 3.
CT scan showing intracerebral hemorrhage affecting the cortex in a patient who presented with seizures. The anterior lucency is an imaging artifact.

Figure 4.
CT scan showing extensive, thick accumulation of subarachnoid blood in the cisterns. Image kindly provided by Dr Jose Biller.

Table 1

Factors Associated with Childhood Non-Traumatic Intracranial Hemorrhage

Risk Factor	Source 1	2	3	4	5	6	7	8	9	10	Total
Idiopathic	29	12	11	7	1	4	3	6	14	7	94
Arteriovenous Malformation	36	11	23	23	10	18	8	13	9	5	156
Aneurysm	15	2	4	4	3	5	1	4	1		35
Cavernous Malformation	17	7	2	2		2	4	9		1	42
Venous Angioma		2					1				3
Arachnoid Cyst									1		1
Tumor	3	12	1	9	4	1	2	5	1	8	46
Medical	16	23	16	26	6	4	2	8	4	8	113
Total	116	69	51	71	24	34	21	45	30	29	490

Neurosurgical series or series that excluded tumors were not included.

Sources: 1¹⁶, 2⁷, 3⁷⁴, 4⁸, 5⁹, 6¹⁰, 7⁷⁶, 8¹¹³, 9¹¹⁴, 10⁶

Table 2

Factors Associated with Childhood Hemorrhagic Stroke

Source	1*	2	3*	4	Totals
Total	29	42	62	61	194
Arteriovenous Malformation	5	20	23	11	59
Cavernous Malformation	1		2	7	10
Venous Angioma				2	2
Aneurysm			4		4
Moyamoya				1	1
Genetic Coagulopathy	1	1	6	1	9
Acquired Coagulopathy	2	2	4		8
Thrombocytopenia	1	3	8	8	12
Sickle Cell Disease	2		3		5
Meningitis	1	2			3
Encephalitis	1				1
Systemic Infection				3	3
Brain Tumor	8	1	9	11	29
System Malignancy		2		5	7
Hypertension	3				3
Genetic/Metabolic Disease		1			1
Systemic Illness		1	4	4	9
Other			3		3
Unknown	7	9	7	10	33

* These series listed more than one factor per subject: 1,(6) 2,(74) 3,(8) 4(7).

Table 2. This table selects 4 studies from Table 1 that reported the medical potential risk factors in more detail than other studies.

Table 3Clinical Presentation in Children <6 Years of Age with Intracranial Hemorrhage^{*}

Presenting Signs	N (N = 34)	%
Mental Status Changes	18	53
Convulsions	11	32
Vomiting	7	21
Respiratory Distress	4	12
Decreased Movement/Weakness	4	12

^{*} Several cases had subdural hemorrhage.

Table used with permission from Archives of Neurology.⁷

Table 4Clinical Presentation in Children 6 Years of Age Presenting with Intracranial Hemorrhage^{*}

Presenting Signs	N (N = 51)	%
Headache	37	73
Mental Status Changes	29	57
Focal Neurological Signs	20	39
Nausea or Vomiting	17	33
Convulsions	8	16
Miscellaneous	12	24

^{*} Several cases had subdural hemorrhage.

Miscellaneous symptoms = dysphasia; fever; dizziness; stomach, neck, or ear pain; bradycardia; respiratory arrest; abnormal gait)

Table used with permission from Archives of Neurology.⁷