Therapeutic Approaches and Advances in Pediatric Stroke

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Summary: Evidence-based therapeutic interventions for pediatric ischemic cerebrovascular disease are beginning to emerge. The primary therapeutic target is usually the pathological prothrombotic disturbance that underlies the majority of pediatric stroke. A battle between anticoagulation and anti-platelet therapies continues to provide controversy and is the inspiration for upcoming randomized trials. Supportive care and neuroprotective strategies are an important consideration in children with stroke. Attempts to determine the safety of acute thrombolytic interventions are also underway. Finally, unique medical and surgical treatments for specific diseases leading to stroke in children continue to evolve. After briefly summarizing the epidemiology, pathophysiology, diagnosis, and outcomes of ischemic strokes in children, treatment approaches and alternatives will be reviewed in detail with emphasis placed on current areas of controversy and future directions for clinical research.
Key Words: Cerebrovascular disease, pediatric stroke, child, anticoagulation.

INTRODUCTION AND EPIDEMIOLOGY

Stroke is a common cause of neurological disease in children and ranks in the top ten causes of death in infants.[1,2] Studies from the last two decades estimate an incidence of 2-8/100,000 children/year and, in neonates, 1:4000 live births.[3,4] The current review will focus on ischemic stroke, consisting of arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT), emphasizing treatment aspects. For detailed coverage of ischemic and hemorrhagic stroke the reader is referred to recently published reviews.[4,5,6]

AIS comprises infarction in a focal arterial distribution resulting from occlusion of cerebral arteries. CSVT is defined as thrombotic occlusion of cerebral veins or sinuses, and is associated with venous infarction, either bland or hemorrhagic, in about 50% of cases. In children the proportion of AIS to CSVT is approximately three to one, and in neonates is two to one where the incidence of both is highest. Recurrence rates are highest in older infants and children with AIS where the risk approaches 25-30%.[7] The life-long morbidity of stroke in a child lasts decades, amplifying its impact on society and the quality of life of a child and their family.

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RISK FACTORS AND PATHOPHYSIOLOGY

In the newborn period, AIS has distinct associations including acute systemic insults, maternal or obstetrical factors, and prothrombotic states definable in about two-thirds of infants.[3,6,8] In older infants and children, risk factors are identified in 70 to 90% of children.[3,9,10,11] About half of children have no prior significant medical history.[11] While over 100 different risk factors for pediatric stroke have been suggested,[7] causal relationship to AIS has not necessarily been proven. In pediatric AIS, arteriopathies, cardiac disease, and prothrombotic disorders are the most commonly identified risk factors.

Arteriopathy refers to disorders of cerebral arteries that predispose to stroke and account for over 50% of AIS in older children.[9,11,12] Arterial dissection may be related to trauma or can occur spontaneously in both the anterior and posterior circulations.[13,14] Moyamoya describes the "puff of smoke" appearance on angiography created by collateral vessels that develop secondary to a bilateral, progressive, proximal, non-inflammatory arteriopathy of the distal internal carotid artery.[15] Moyamoya can be idiopathic or secondary to a long list of both acquired and inherited conditions. Children with sickle-cell disease (SCD) stroke due to moyamoya, chronic

arteriopathy, and acute crises.[16] Over 20% of children with SCD will have a stroke and recurrence is common.[17]

Inflammatory arteriopathy can be isolated to cerebral vessels. A monophasic, self-limited form termed transient cerebral arteriopathy of childhood (TCA) is a common cause of AIS in children.[11,12,18,19] When TCS occurs less than 12 months after chicken pox, it is termed post-varicella angiopathy.[11,20,21] Isolated angiitis of the CNS (IACNS) affects multiple-sized cerebral vessels without evidence of systemic involvement.[22,23,24] A variety of systemic vasculitides and collagen vascular diseases are also associated with pediatric stroke.[24,25] Both AIS and CSVT are associated with bacterial meningitis, particularly in neonates and young infants.[26] Children with HIV can develop a diffuse vasculopathy that may be virus-mediated.[27] Fibromuscular dysplasia[28] and post-radiation vasculopathy[29] are rare non-inflammatory vasculopathies. Other vasospastic disorders include migranous and drug-induced infarction.[30,31]

Cardiac diseases are a common predisposing factor for pediatric stroke including congenital malformations, cardiomyopathies, endocarditis, and arrythmias. Diagnostic and interventional catheterization exacerbate the risk.[6,11,32,33,34] Any potential right-to-left shunt carries a risk of paradoxical thromboembolic stroke.[35]

Prothrombotic disorders, both congenital and acquired, have been associated with 20-50% of strokes in children.[7,8,36] Prothrombotic abnormalities of both the mother and fetus have been associated with perinatal AIS.[6,37] Other hematological disturbances associated with pediatric stroke include iron-deficiency anemia[11,38] and polycythemia.[39]

In neonates, peripartum factors such as preeclampsia, prolonged rupture of membranes, and placental abnormalities are risks.[6,40] In older children, metabolic disorders may produce stroke or stroke-like episodes including MELAS,[41] Fabry disease,[42] and hyperhomocysteinemia.[11] Neurocutaneous syndromes associated with pediatric stroke include tuberous sclerosis, neurofibromatosis type 1, epidermal nevus syndromes, incontientia pigmenti, the and the PHACES syndrome.[43,44] Metabolic derangements of childhood diseases can result in cerebral infarction, including diabetic ketoacidosis[45] and nephrotic syndrome.[46]

Physiological features including slower blood flow and a greater role of the coagulation system in thrombus formation are particularly important in CSVT pathophysiology. Venous congestion leads to focal cerebral edema progressing to venous infarction and hemorrhage. The superficial sinovenous system is involved twice as often as the deep system, multiple locations affected in nearly 50%, and infarction occurs in over 40% with two-thirds of these being hemorrhagic.[47] The most common risk factors for CSVT are dehydration and prothrombotic disorders with others including infection, trauma, cancer/chemotherapy, and systemic disease.[47,48,49]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis of AIS and CSVT is suggested by clinical presentations which are age-dependent. Approximately half of perinatal AIS will present acutely, usually as seizures, while focal deficits such as hemiparesis are uncommon.[6] Most remaining children are diagnosed later in childhood, often within the first year, when hemiparesis or seizures are recognized.[8] Older children usually present with hemiparesis due to middle cerebral artery territory events. Infarcts are frequently isolated to the basal ganglia,[3] with resultant movement disorders either at presentation or beginning within several months.[50] Posterior circulation strokes account for less than 10% of cases.[51] Compared with adults, seizures, fever, and headache are more common.[52,53] Children with CSVT tend to present gradually with diffuse neurological dysfunction, seizures, or symptoms of increased intracranial pressure.[47,54]

History for the neonate with stroke should screen for complications during pregnancy or the perinatal period, the older child for trauma, infection, drug exposure, hematological or cardiac disease, and both for family history. Transient ischemic attacks (TIA) probably occur regularly in children with stroke but have not been well studied. Stroke mimics include migraine, seizures, hypoglycemia, demyelination, and functional disorders. Lengthy delay in diagnosis of stroke in children is common.[55] Children with suspected stroke should be seen urgently at a tertiary care pediatric care center with access to a multidisciplinary team headed by a pediatric neurologist. All children require measurement of coagulation parameters, blood cell counts, and routine blood work as well as a detailed prothrombotic work-up.[56] Echocardiography with agitated saline bubble study and cardiology evaluation is required. Imaging of the brain and cerebral vasculature is mandatory. Clinical indications may dictate additional investigations.

Multiple neuroimaging modalities are useful in the diagnosis of pediatric stroke. Computed tomography (CT) can diagnose larger infarcts outside the hyper-acute timeframe and rule-out hemorrhage. MRI, particularly diffusion weighted studies, offer high diagnostic sensitivity and specificity with the concomitant vascular imaging required in all children.[6,57] MR angiography (MRA) can detect most large vessel vasculopathies in children.[58,59] Advanced neuroimaging technology is providing unique avenues to explore the mechanisms of stroke in children and the response of the developing brain to injury. Cranial ultrasonography has limited sensitivity in detecting perinatal strokes.[60] Transcranial Doppler ultrasound (TCD) can predict the risk of stroke

and guide therapy in children with SCD.[61] Cerebral angiography remains the gold standard for neurovascular imaging in children, and may be required for certain diagnoses.[9,13,24,59]. Radiological diagnosis of childhood CSVT is challenging and is reviewed elsewhere. [62] CT venography (CTV) provides a quick and accurate diagnosis of CSVT but contrast MR venography (MRV) offers comparable accuracy and provides assessment of brain parenchyma while avoiding radiation.[63]

OUTCOME

Outcomes from pediatric stroke are well defined but accurate early predictors remain elusive. Many children with hemiplegic cerebral palsy (CP) and a smaller proportion with bilateral CP have had a perinatal stroke.[6,64] In symptomatic perinatal stroke, mortality rates are 10-fold higher compared to older children[1] and neurological deficits or epilepsy occur in 50-66% of survivors.[3,40,65,66] Deficits include sensori-motor, language, visual, cognitive and behavioural problems.[3,40,65,66]. The outcome from stroke in infancy is often assumed to be better than that for older children, which is in turn better than adults,[6,65] a finding often attributed to increased "plasticity" though proof of this and an understanding of the mechanisms that might underlie it are lacking.

More than half of childhood AIS survivors will live with moderate to severe disabilities [67,53,68] and case fatality rates range from 5% to 28%.[53,67] Motor deficits are most frequent, followed by communication disorders and neuropsychiatric, cognitive, and behavioural complications.[67,68,69,70,71] Epilepsy complicates at least 15% of childhood stroke,[72,67] hyperkinetic movement disorders may be disabling,[73,74] and headache disorders occur in one-third of cases.[67] Compared with AIS, outcome is generally better after CSVT. In the largest prospective study, 65% of 160 infants and children with CSVT were normal though the mortality rate approached 10%.[47] The remaining third had significant neurological deficits that often worsened over time and 20% of survivors had epilepsy. Other studies have reported comparable outcomes.[54,67,75] Decrease in quality of life is present in over half of stroke survivors, affects the entire family,[76] and relates to both neurological deficits and psychosocial factors.[77]

TREATMENT AND PREVENTION

While the evidence for most treatment approaches in pediatric stroke is desperately short, some consensus regarding therapeutic strategies is emerging from multicenter collaborations with areas of divergent opinion providing opportunities for randomized controlled clinical trials (RCCT). With the exception of SCD, best available evidence is based on theory, extrapolation from adult studies, and case-control or cohort studies in children. Completion of the most pressing RCCT's is a top priority in childhood stroke research and international collaborations have been established and are currently facilitating their initiation. Two separate, evidence-based treatment guidelines have recently been published and are referred to here as the *Chest*[78] and UK guidelines[79] respectively. Both were created by panels that included pediatric neurologists and hematologists from multiple centers. While attempting to be evidence-based, most recommendations receive the lowest affirmative grade of support due to the lack of RCCT. Both publications acknowledge these limitations and stress that treatment must always be tailored to individual patients in accordance with best clinical practice. These guidelines have been compared and contrasted in detail elsewhere.[80] The following review of pediatric stroke treatment follows a chronological approach from hyperacute (hours) to acute (days), subacute (weeks to months), and chronic (years) interventions.

Hyperacute Treatment: Thrombolysis

Intravenous and intra-arterial thrombolysis, now routine in adult stroke, remains anecdotal in children.[81,82,83,84,85] In adults the absolute risk reduction for poor outcome is approximately 15% with thrombolysis, with a number needed to treat of 7-8 in the largest RCCT.[86] Careful patient selection and adherence to protocol are critical to optimize the risk:benefit balance of thrombolytic therapy in adults[87,88] but no studies in pediatric stroke have been completed..

Numerous barriers must be overcome before hyperacute therapies can be applied to children. Foremost is determining if differences in stroke mechanisms, and vascular and coagulation systems confer advantages or risks for thrombolysis. Limited access to timely treatment is highlighted by a study from an experienced stroke center where fewer than 25% of pediatric cases were diagnosed within the 3-6 hour time window.[55] Improved education of primary care physicians and the public are required to overcome this delay to diagnosis. The broad differential diagnosis for acute neurological deficits in children requires rapid but definitive neuroimaging protocols to confirm infarction and arterial occlusion. Finally, measures of acute stroke severity to identify patients at risk of poor outcome are required and a pediatric modification of the NIH stroke scale, the Ped-NIHSS, is currently in development.

Hemorrhage is the primary concern with thromboytic use though recent evidence suggests that younger age and careful patient selection minimize the risk in adults.[88] Tissue plasminogen activator (tPA) administered to children for non-cerebral thrombosis has shown good success in clot lysis but major bleeding in 11% and intracranial hemorrhage in 1-2%.[89] Alternative acute in-

terventions including mechanical clot manipulation and cerebral angioplasty have only been described in isolated pediatric cases.[84,90] In the case of severe CSVT, the role of catheter-introduced administration of thrombolytics agents remains controversial and could be considered a last resort for children with severe, progressive disease who are failing systemic anticoagulation.

Due to the theoretical risks and lack of evidence, neither the UK nor *Chest* guideline recommends the use of thrombolytics in pediatric stroke.[78,79] However, there is reason to believe that the non-standardized use of thrombolytics in children occurs regularly. Therefore, a safety and feasibility pilot study for the use of intravenous or intrarterial tPA in children six years or older presenting early with severe AIS and proven arterial occlusion has recently been initiated at several North American centers.

Acute and Subacute Treatment: Anti-platelet versus anti-coagulation

Therapies directed at the inhibition of either platelet or coagulation cascade function play a role in the acute, subacute, and chronic phases of pediatric stroke treatment. Substantial differences exist between adult and pediatric platelet, coagulation and vascular systems[91] and, hence, stroke pathophysiology and approaches to treatment. A disturbance of the coagulation system is supported in CSVT and AIS secondary to arterial dissection, cardiogenic thromboembolism, prothrombotic states, paradoxical embolism, or severe (slow flow) arterial stenosis. Most other vasculopathies and many idiopathic strokes more likely involve platelet-mediated mechanisms. Population-based studies suggest more than half of children with AIS will receive at least one of aspirin (ASA), unfractionated heparin (UFH), low molecular weight heparin (LMWH), or warfarin although the indications appear to range widely and issues of dosing and duration are unresolved.[3] Good evidence supports the safety of all of these agents in children with stroke.[3,92,93,94]

Anticoagulation therapy (ACT) is not supported by evidence for the early treatment of most arterial strokes in adults. However, differences in the pathophysiology of the most common causes of pediatric AIS underlie support for the use of early ACT. A decision to treat must balance estimated benefit of preventing further strokes or thrombus propagation against risk of hemorrhage. Contraindications to ACT include significant hemorrhagic transformation, uncontrolled hypertension, or known bleeding disorder.[78] Options for acute ACT generally include heparin or LMWH while continuation of LMWH or oral ACT with coumadin are the alternatives for the subacute timeframe. The advice of a thrombosis expert is invaluable in the management of anticoagulated pediatric stroke patients.

Heparin inhibits the coagulation cascade at multiple sites but most prominently by inactivating thrombin via activation of antithrombin.[95] Age-dependent differences in both thrombin and antithrombin levels complicate heparin ACT in young children, particularly neonates.[96] Maintenance dosing recommendations are as follows: infants under 12 months (28 units/kg/hr), older children (20 units/kg/hr), and adolescents (18 units/kg/hr).[78] An initial bolus is usually not given to reduce a theoretical risk of increased hemorrhage. APTT are monitored for dosing adjustments with a target of 60-85 seconds though heparin levels may also be employed.[96] Early complications of heparin include hemorrhage and heparin-induced thrombocytopenia which occurs in less than 4% of cases.[97]

Low molecular weight heparins (LMWH) are smaller molecular subcomponents of UFH and are emerging as the preferred agent for subacute, and possibly acute, ACT in children with stroke. Advantages of LMWH include subcutaneous administration, reproducible pharmacokinetics, and a better safety profile with a low rate of hemorrhage.[92,94,98] Monitoring is easier with less frequent measurement of anti-factor Xa levels. Drawbacks include less predictable anticoagulation compared to adults and relative lack of reversibility.[78] Several varieties of LMWH and dosing schedules are described elsewhere.[78] Enoxaparin is the most commonly used variety and typical treatment dosing is 1.5 mg/kg daily in infants under 2 months and 1.0 mg/kg daily in older children.[78]

The clearest discrepancy between the UK and *Chest* guidelines is the initial choice of acute therapy for AIS. The *Chest* supplement supports early initiation of ACT with either LMWH or UFH for the first 5-7 days and until a cardiac source or dissection has been excluded.[78] Children are usually then changed to ASA (3-5 mg/kg/d) or, in cases due to cardiogenic embolism or dissection, remain on ACT (coumadin or LMWH) for at least 3 months. In contrast, the UK guideline recommends the initiation of ASA at 5 mg/kg/day except in patients with contraindications of intracranial hemorrhage or SCD.[79] Early ACT is supported only in cases of proven arterial dissection and is considered in suspected cardiac thromboembolism. Early treatment of neonatal AIS treatment is even less studied and was not addressed by the UK guidelines. The use of ACT with UFH or LMWH for 3 months in neonates with definitive cardioembolic source is supported by the *Chest* guideline.[78] The only other well supported acute intervention is the use of exchange transfusions to lower hemoglobin S concentrations to less than 30% in children with SCD and stroke.[79]

Several important differences in CSVT pathophysiology dictate differences in early treatment. Venous thrombosis is often gradual and progressive, evolving from venous congestion to infarction with possible hemorrhage. Slow flow heightens the role of the coagulation

system and allows thrombus progression over time. Closer parallels likely exist between adult and pediatric CSVT where risk factors and pathophysiology are similar. Consistent evidence supports ACT with heparin in adult CSVT for preventing death and improving neurological outcome, even among patients with initial evidence of bleeding.[99,100,101] Good safety profiles for LMWH, UFH, and warfarin have been documented in both neonates and children with non-hemorrhagic CSVT.[47,93,102]

The *Chest* guidelines recommend ACT in children with CSVT and in neonates without major hemorrhage.[78] Initial therapy with either heparin or LMWH is continued for 5-7 days then changed to LMWH for ongoing therapy. For neonates, the duration is usually 6-12 weeks while in older children, checkpoints are set at 3 and 6 months. Repeat venous imaging is performed at the earlier time point and ACT is discontinued if full recanalization has occurred or is continued to the second time point if it has not. Oral ACT with coumadin is an alternative for older children though a comparison to LMWH has not been performed. In the case of large initial hemorrhage that prevents initiation of ACT, repeat imaging at 5-7 days is indicated to determine if thrombus propagation has occurred in which case ACT should then be considered. In the case of continued clot progression on maximal ACT, systemic or regional thrombolytic therapy can be considered though this is not well studied in adults[103] and has only been reported anecdotally in children.[104,105] Additional early treatments for pediatric CSVT include supportive measures (see below) as well as antibiotic therapy for septic thrombophlebitis, and management of increased intracranial pressure or hydrocephalus. Current issues to be resolved in the treatment of pediatric CSVT include the risk of treating large hemorrhagic infarcts, the ideal duration of therapy, neuroimaging endpoints to guide therapy, and a comparison of heparin versus LMWH.[80]

Acute Treatment: Supportive Care and Prevention of Secondary Brain Injury

Early supportive care is essential to prevent secondary brain injury in children with stroke.[106] Based primarily on adult evidence,[107] this includes normalization of blood sugar, temperature, ventilation/oxygenation, blood volume and blood pressure. Both hyper- and hypoglycemia are associated with poor outcome and larger infarcts.[108,109] The theoretically protective effect of hypothermia (*reviewed in this volume*) has not been proven in focal ischemic brain injury in children though hyperthermia likely exacerbates injury[110] and infection should be aggressively treated. Seizures may worsen ischemic brain injury[111] and should be treated promptly. Improved understanding of the cellular and molecular processes that mediate ischemic brain injury has lead to numerous trials of potential neuroprotective therapies in stroke[112] though results have been disappointing. Neuroprotective therapies face additional challenges in pediatric stroke where manipulations of cellular biology may have unwanted effects on brain development.[64]

Malignant cerebral edema is a significant complication of large strokes, and a greater ratio of brain tissue to intracranial volume exacerbates the problem in children. Intracranial pressure monitoring, mannitol or hypertonic saline may be unsuccessful, and evidence supporting emergency decompressive craniectomy is emerging.[113] The procedure may be life-saving if done early in cases of impending herniation, is associated with good outcomes in young stroke patients,[114] and is supported by published guidelines.[79] Anticipated surgical intervention for malignant cerebral edema might also influence the acute treatment choice towards the more easily reversible UFH rather than LMWH or ASA. Additional supportive treatment issues including prevention of aspiration, nutrition, skin care, and DVT prophylaxis should be considered. Care in a tertiary pediatric center with access to relevant specialists and investigations should be considered the standard[79] as specialized stroke care has been shown to improve outcomes in adults.

Chronic Treatment: Secondary Stroke Prevention

Recurrence rates for pediatric AIS range from 10-25% in treated, and as high as 50% in untreated children outside the neonatal period.[9,10,115,116] Recurrence risk is maximal in the first six months, and is increased in the presence of vasculopathy or multiple risk factors.[9,10,56] Certain prothrombotic disorders[56] carry an increased recurrence risk while others do not.[117] In perinatal AIS recurrence rates are less than 5%.[67,118] The first RCCTs of secondary prevention in pediatric AIS are now in development. Primary prevention opportunities include children undergoing cardiac surgery and mothers at increased risk for fetal stroke.

Anti-platelet treatment, usually with aspirin (ASA), is the current mainstay for long-term prevention of recurrent AIS in children. Adult studies indicate that low dose ASA treatment provides a 25% risk reduction[119,120] and is equivalent to vitamin K antagonists for stroke prevention outside of atrial fibrillation.[121] A prospective, nonrandomized study of children with AIS on either ASA or LMWH demonstrated a failure rate of approximately 10% in children selected by clinicians for each therapy.[94] Both the UK and *Chest* guidelines support the use of ASA for secondary stroke prevention in most cases of childhood AIS with recommended doses ranging from 1-5 mg/kg/day[78,79] which appear safe in children.[94,122] Side effects of ASA are minimal at low doses and include gastric upset and easy bruisability. Significant hemorrhage is rare and Reye syndrome is not reported

with low dose ASA, however reduction of dosage during febrile illness or influenza vaccination is recommended.

For children with non-vasculopathy strokes, the guidelines disagree on the use of long-term ASA[78,79] and such areas of clear equipoise will likely serve as starting points for upcoming RCCT.[80] Measurement of ASA efficacy via platelet functional assays may help predict the success or failure of preventative therapy.[123] Preliminary evidence for the safety and indications of other anti-platelet agents such as clopidogrel in pediatric stroke is emerging.[124] In the situation of recurrent stroke in a patient already on anti-platelet therapy, the UK guideline suggests consideration of ACT[79] while this issue was not addressed in the *Chest* publication.

ACT is considered for long-term prevention in children with AIS with high risk heart disease or severe prothrombotic disorders. Supporting evidence comes from the Warfarin-Aspirin Recurrent Stroke Study-(WARRS)[121] where a subgroup analysis of "cryptogenic" strokes (not due to atherosclerosis, atrial fibrillation, or lacunar infarction), a group more similar to pediatric AIS patients, demonstrated a significant benefit of ACT over ASA in secondary stroke prevention. Warfarin is a vitamin K antagonist that inhibits production of multiple components of the coagulation cascade. Approximately 72 hours of oral warfarin is required for effect and a target INR of 2-3 is appropriate for most children. The initial dose is 0.2 mg/kg with subsequent dosing adjustments based on published nomograms.[78] Advantages of effective anticoagulation and oral administration are offset by complications of regular monitoring and risks of drug interactions. Special consideration regarding vitamin K levels are required in breastfed infants, children with gastrointestinal disease, and those on total parenteral nutrition. The theoretical increased risk of hemorrhage related to higher physical activity in children is probably small though this has not been studied and recommendations against high-risk activities such as contact sports are suggested.

Education and family support are important.[79] Attention to psychosocial complications and development of educational and supportive resources are important areas of progress in pediatric stroke care. The use of alternative therapies, including several with potential to influence coagulation, is common in children with stroke from certain cultural groups and should be inquired about.[125]

Disease-Specific Therapies

In the only RCCT in pediatric stroke to date, the STOP trial demonstrated a 92% risk reduction for SCD children receiving regular blood transfusions.[61] All SCD children with clinical or neuroimaging evidence of cerebral ischemia or those who demonstrate intracranial stenosis on TCD (velocities $>$ 200 cm/sec) should receive blood transfusions every 3-6 weeks to maintain hemoglobin S levels below 30%.[78,79] Annual screening for cerebral vasculopathy with TCD is recommended from age three years but optimal duration of therapy and whether asymptomatic children with normal velocities would benefit from transfusions is unknown. Anti-platelet or anticoagulant therapies in SCD remain to be assessed.[126] Hydroxyurea therapy may also prevent stroke in SCD.[127] Nocturnal oxygen saturation inversely correlated with risk of cerebral ischemic events and nocturnal oxygen supplementation may be an additional opportunity for intervention.[128]

Treatment of moya moya disease (MMD) presents unique challenges and controversies. There are no proven medical therapies though a theoretical acid-base sensitive vaso-reactive mechanism that may underlie AIS in children with moya moya[129] has lead some to treat with carbonic anhydrase inhibitors. Patients are often treated with long-term ASA though this is unproven and must be balanced against a shifting risk toward hemorrhagic stroke with advancing age in MMD. A wide variety of surgical therapies have been employed though supporting evidence is only just emerging. In direct procedures, extracranial blood vessels such as the superficial temporal artery, are anastomosed to distal portions of intracranial vessels, usually the middle cerebral artery (MCA). Indirect procedures introduce new vascular supply to tenuously perfused brain by relocating extra-cranial arteries or vascularized tissues such as muscle to the overlying meningeal surface. Combined direct and indirect procedures may maximize cerebral collateralization.[130] Recent evidence suggests that younger age of onset may carry a higher risk of recurrent stroke and worse outcome and promotes early surgery.[131] Surgery–related infarctions occur in approximately 5-10% of cases.[130,131]

Other disease specific therapies include immunosuppression with steroids, cyclophosphamide, or other agents for progressive cerebral vasculitis.[24] A role for acyclovir in post-varicella angiopathy remains theoretical. Stroke secondary to inborn metabolic errors may be treatable with enzyme replacement in Fabry disease, vitamin therapy in homocystinuria, and "cocktail therapy" for MELAS.

Preventative care includes attention to modifiable risk factors to reduce future stroke risk. Recommendations include regular exercise, a balanced diet, and avoidance of smoking. Children with stroke and a prothrombotic disorder should be counseled to avoid episodic dehydration and prophylactic dosing of anticoagulation in high-risk situations has been suggested. Oral contraceptives and vasoconstrictor agents such as triptans, ergots, or sympathomimetics should be avoided.

Early, aggressive multimodal rehabilitation therapy including physical, occupational, and speech modalities is essential in the treatment of all children with stroke.[79]

The constant evolution of the developing brain complicates the formal evaluation of rehabilitation strategies in pediatric stroke patients. Most rehabilitation studies have focused on motor function as it is the most common deficit and the most amenable to evaluation. An RCT has demonstrated the effectiveness of constraint-induced therapy in children with congenital hemiplegia.[132] Other strategies including inhibitive casting, lycra splinting, treadmill training, and functional electrical stimulation remain to be studied in pediatric stroke. The UK guidelines recommend muscle strengthening to improve function and minimize contractures, Botox injections for spasticity, and ankle-foot orthoses for gait and contracture prevention.[79]

Formal neuropsychological evaluation is required to document cognitive and behavioural deficits and determine educational resource and environment needs. Serial assessments may be required as development proceeds or in children with recurrent events. Language difficulties are common and speech-language therapy may be required. Tailoring of interventions to an individual child's lifestyle, goals, and level of functioning should be integrated with school and home environments.[79]

Summary

An evolution in the approaches to treatment of pediatric stroke has paralleled other recent advances in clinical research. A multitude of current interventions are likely improving outcomes but definitive evidence is still lacking in most circumstances. Established international collaborations will provide the power required to conduct the most pressing clinical trials in the near future and begin to clarify the best therapies for children with stroke.

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