Hemorrhagic stroke in children

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ABSTRACT

Hemorrhagic stroke (HS) in childhood accounts for almost 50% of childhood strokes, is among the top ten causes of deaths, or determines lifelong disability. These facts form significant socio-economic and demographic problems. The purpose of this review is to analyze current knowledge about HS in children. The data on HS terminology are presented, taking into account the International Classification of Diseases 11 edition. Attention is paid to the epidemiology of HS in children, including the results of individual local studies. The risk factors of HS in children were studied with an analysis of the causal, pathophysiological mechanisms of HS of various etiologies. The ideas about the clinical manifestations of HS in children are described. The analysis of HS treatment in children was carried out with an emphasis on achievements in neurointensive therapy of the acute period of HS. This review also includes information on the outcomes of HS in children.

KEYWORDS: Hemorrhagic stroke in children, epidemiology, risk factors, clinic, treatment, outcome

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Introduction

Hemorrhagic stroke (HS) in childhood requires careful study, as it is not uncommon, determines high mortality and disability of children. The importance of the problem is emphasized by the high social significance, as well as the lack of awareness of HS among doctors of various pediatric specialties. There are few studies of HS in childhood. There is limited information on risk factors, clinical and radiological correlation, and HS outcomes in children. There are no clear recommendations for working with such patients, proven, generally accepted diagnostic and treatment strategies. The purpose of this review is to analyze current knowledge about HS in children. We conducted a literature review in publications without language restriction by keywords: hemorrhagic stroke in children, definition, terminology, classification, epidemiology, risk factors, clinic, treatment, outcome of HS in children.

Terminology of Hemorrhagic Stroke in Children

HS occurs as a result of bleeding from the cerebral vessels.[1,2] In 1995 the World Health Organization has proposed the definition of stroke as "rapidly developing clinical signs of focal (or global) brain dysfunction, symptoms of which last 24 h or longer or lead to death for no apparent reason other than vascular origin".[3]

In the International Classification of Diseases (ICD) 11 edition, HS types are presented in Chapter 08 - Diseases of the nervous system, section "Cerebrovascular diseases" 8B0-8B2, heading "Intracranial hemorrhage" 8B00 - 8B0Z The complete block of Intracranial hemorrhage non-traumatic etiology in ICD-11 is presented in Table 1.

Thus, the ICD 11 edition reflects, first of all, the anatomical site of bleeding. Thus, subarachnoid (SAH) hemorrhage is characterized by extravasation of blood between the inner, "spider" membrane and the substance of the brain. Intracerebral (ICH) bleeding is characterized by hemorrhage into the parenchyma (IPH) or ventricles of the brain (IVH). Subdural hemorrhage is bleeding between the soft and dura mater. There are also indications of hemorrhages lobar, hemispheric, in the brainstem and cerebellum of the brain.

In childhood, such characteristics of HS are also relevant, such as pediatric or pediatric stroke (occurs in children aged 29 days to 18 years), as well as neonatal or perinatal stroke: develops from the 20th week of pregnancy on the 28th day of the child's life.[4–6]

Epidemiology of Hemorrhagic Stroke in Children

Jordan L.C. estimates that almost 50% of childhood strokes are hemorrhagic.[7–9] Other authors present the average incidence of HS among children in the range of 1 - 13 per 100 000 children per year.[8–12] The incidence of HS in children in the USA is 4.1 per 100 000, in the UK - 2-5 per 100 000, in France - 2.9 per 100 000, in Sweden - 2.1 per 100 000 children per year.[5,8,13–15] Among Hong Kong children, the incidence of HS is at the level of 28% of children per year, in Saudi Arabia - 10%.[16,17] HS is more common in children under the age of two. In this case, about 40% of all HS cases develop at the 1st year of life and peak

Table 1. Intracranial haemorrhage non-traumatic etiology.

8B00	Intracerebral haemorrhage
8B00.0	Deep hemispheric haemorrhage
8B00.1	Lobar haemorrhage
8B00.2	Brainstem haemorrhage
8B00.3	Cerebellar haemorrhage
8B00.4	Intraventricular haemorrhage without parenchymal haemorrhage
8B00.5	Haemorrhage of multiple sites
8B00.Z	Intracerebral haemorrhage, site unspecified
8B01	Subarachnoid haemorrhage
8B01.0	Aneurysmal subarachnoid haemorrhage
8B01.1	Non-aneurysmal subarachnoid haemorrhage
8B01.2	Subarachnoid haemorrhage not known if aneurysmal or non-aneurysmal
8B02	Nontraumatic subdural haemorrhage
8B03	Nontraumatic epidural haemorrhage
8B0Z	Intracranial haemorrhage, unspecified

in the perinatal period.[18] Data from Laugesaar R., et al, shows that perinatal HS occurs with a frequency of 63 cases per 100 000 live births.[19] Carolei A., et al, and Cardo E., et al, revealed that in the 1st month of life there are 28.6 cases of HS per 100 000 newborns among those born before the 31st week of gestational age and 24.7 cases among those born at a period of more than 31 weeks.[20,21] Other authors present the frequency of perinatal HS in the range of 26.4 - 40.0 per 100 000 live births per year.[4,11,22–24] The indicators of HS frequency in children are presented in Table 2.

There are studies indicating the frequency of ICH and SAH. ICH (Figure 1) occurs with a frequency of 0.71 - 1.4 per 100 000 children.[8,25] SAH is 18-22% (Figure 2).

The combination of ICH and SAH occurs in 32% of cases.[16,26,27]

The distribution of HS by gender in most studies indicates that boys have a higher risk of stroke than girls by about 28%. The ratio of boys and girls with HS is 1.2 - 1.5:1.[8,10,16,28]

Risk Factors for Hemorrhagic Stroke in Children

Cerebrovascular Pathology and Hemorrhagic Stroke in Children

The most common cause of HS in children is cerebrovascular pathology. Thus, Beslow L.A., et al, found that vascular system abnormalities caused 91% of HS cases in children.[29] Other authors claim that cerebral vascular abnormalities are detected in children with HS in 32.2% - 67% cases.[28,30–34] Abnormalities of the vascular system include arteriovenous malformations (AVM), intracranial aneurysms (IA) and cavernous malformations (CM). In studies by Jordan L.C., et al, pediatric HS, 31% of patients had cerebral AVM, IA - 13%, CM - 15%.[26] Giroud M., et al, among 23 children with HS, 9 had AVM, 2 had IA, and 5 had CM.[35]

Vascular abnormalities in most cases are represented by AVM.[36] AVM is a vascular pathology in which veins and arteries intertwine with each other to form a “vascular tangle”. The peculiarity of this vascular formation is that there are no capillaries in it. In this regard, blood from the arteries directly enters the veins, tissues do not receive nutrients and oxygen from the blood, there is no metabolism.[37,38] Lin C., et al, consider AVM as the leading cause of hemorrhage in children with spontaneous ICH.[39] A study of spontaneous ICH in children showed that vascular malformations cause bleeding in 91% of subjects, in studies by Meyer-Heim A.D., et al, in 47% of children.[29] In 53% of patients, hemorrhage occurred as an acute event, and in 47% of cases, a prolonged course of AVM was observed.[32] Al-Jarallah A., et al, revealed a congenital vascular anomaly in 42.6% of children with non-traumatic intra-parenchymal hemorrhage. In 33.8% of cases, there was AVM or fistula.[31] Krings T., et al, state that the probability of the first cerebral hemorrhage in AVM is 2-4% per year.[40] Studies by Carlin T.M., et al, in 96% of cases revealed AVM in children under 5 years of age.[41] Earley C. J. et al, showed that AVM was the cause of ICH in 29% of cases.[25] Gabriel R.A., et al, Plummer N.W., et al, found that AVM determines 8.6% of non-traumatic SAH and 1% of cerebral strokes.[42,43] One bleeding in AVM is accompanied by a mortality rate of 25%.[44]

The next common abnormality of the vascular wall, accompanied by HS, is IA - deformation of the cerebral arteries

Table 2. Indicators of HS frequency in children.

AUTHOR, YEAR OF PUBLICATION	THE FREQUENCY OF CHILDHOOD HS
Broderick J., et al. 1993[8]	1.3 - 1.55 per 100 000 children per year
Lehman L.L., et al. 2018[12]	1 - 1.7 per 100 000 children per year
Giroud M., et al.1995[9]	2 per 100 000 children per year
Lynch J.K., et al. 2002[11]	2-3 per 100 000 children per year
Fullerton H.J., et al. 2003[10]	13 per 100 000 children per year

AUTHOR, YEAR OF PUBLICATION	FREQUENCY OF PERINATAL HS
Cardo E., et al, 2000[21]	24.7 per 100 000 children per year
Lynch J. K., et al, 2001[11]	26.4 per 100 000 children per year
McKinney S.M., et al. 2018[22]	25 - 40 per 100 000 children per year
Laugesaar R., et al, 2007[19]	63 per 100 000 children per year
Armstrong-Wells J., et al, 2009[4]	1 per 2200 - 2800 live births
Takenouchi T, et al, 2012[23]	1 per 6000 - 9000 live births

INDICATORS OF THE FREQUENCY OF HS IN CHILDREN ACCORDING TO THE RESULTS OF INDIVIDUAL LOCAL STUDIES	
AUTHOR, YEAR OF PUBLICATION, COUNTRY	PER 100 000 CHILDREN PER YEAR
Eeg-Olofsson O., et al, 1983, Sweden[15]	2.1
Broderick J., et al, 1993, France[8]	2.9
Zahuranec D.B., et al, 1995, UK[14]	2 - 5
Lynch J.K., 2009, USA[5]	4.1
Al-Sulaiman A., et al, 1999, Saudi Arabia[17]	29.7

in the form of bulging of their walls at the site of thinning. Hitchon P., et al, Gabriel R.A., et al, believe that IA are recorded with a fairly high frequency in the general population: 10.3 per 100 000 per year.[43,45] Huang J., et al, identified 1377 cases of IA. The ratio of boys and girls was 2.2: 1. 11% of aneurysms were formed in the area of bifurcation of the internal carotid artery (ICA), 42% - in the posterior circulation. 37% of the aneurysms were gigantic. In 58% of cases, aneurysms were accompanied by SAH.[46] Sanai N., et al, identified 43 aneurysms in 32 pediatric patients. In 22% of cases, aneurysms were accompanied by SAH. The locations of the aneurysm included the ICA (13 lesions), the middle cerebral artery (11 lesions) and the basilar artery (6 lesions). Of the 43 lesions, 17 (40%) were giant aneurysms, and 22 (51%) had fusiform/dolichoectatic morphological features.[47] Jordan L.C., et al, in the HS study (IPH, SAH and IVH) indicate that aneurysms mainly determine SAH (57%), while among children with pure ICH, an aneurysm was detected in only 2%, and among children with mixed hemorrhage (IPH and SAH) - at the level of 5%. Krings T., et al, confirm that cerebral vascular aneurysms account for 13% of HS, which are mainly manifested by SAH. Aneurysm may be associated with arterial dissection (50%), bacterial or mycotic infections (15%), trauma (5-10%) or idiopathic (30%).[48] Pappachan J., et al, are of the opinion that aneurysms in children with HS are relatively rare, among which 10-15% are post-traumatic and about the same number are fungal.[49]

Another vascular anomaly accompanying HS in children is CA. CA represent intra or extracranial vascular lesions with calcifications. CA occurs sporadically in 13%, and as family cases in 50%. CA develops as a result of cerebral vascular aneurysms, as well as symptomatic hypertension due to kidney diseases, aldosteroma, pheochromocytoma, hypercorticism, and aortic coarctation.[49] CA is the cause of HS in children in 5-15% of cases.[26,50]

Violations of Coagulating and Anticoagulating Properties of Blood and Hemorrhagic Stroke in Children

Al-Jarallah A., et al, among 68 children with intra-parenchymal cerebral hemorrhage, blood clotting disorders were detected in 22 (32.4%) patients.[31]

Prothrombotic or coagulation disorders that lead to the development of HS may be hereditary or acquired.

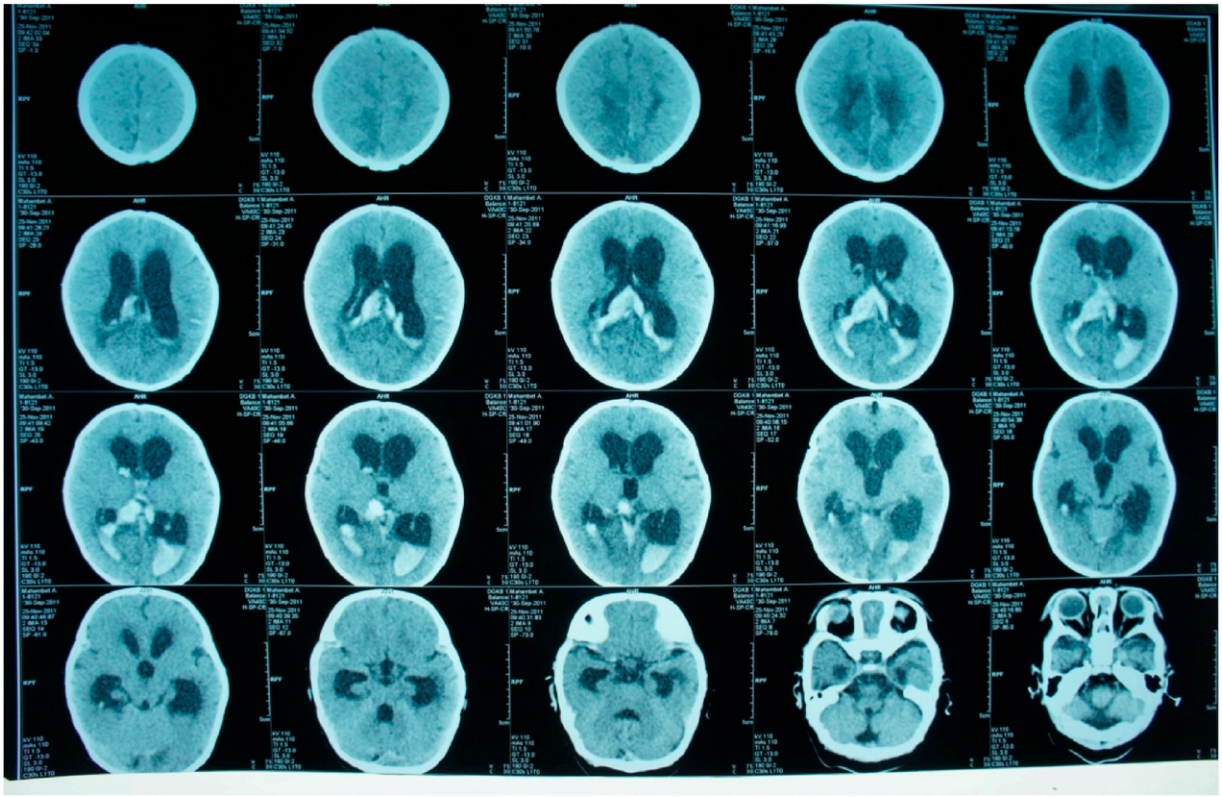

Figure 1. Computed tomogram of intraventricular hemorrhage.

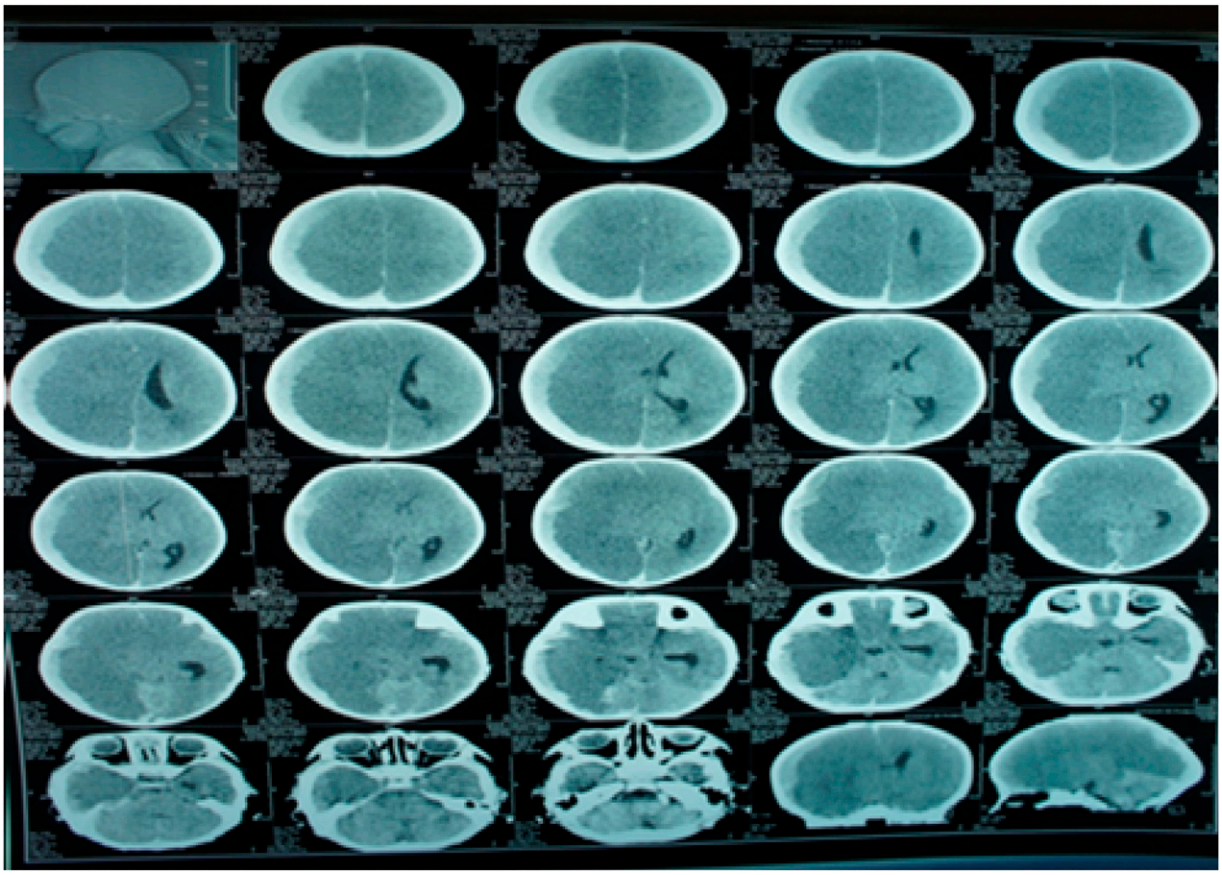

Figure 2. Computed tomogram of subarachnoid hemorrhage.

The most common hereditary prothrombotic abnormalities include deficiency of antithrombin III, antiphospholipid antibodies, plasminogen, prothrombin gene, 20210A VII, VIII coagulation factors (hemophilia).[51–56] Some authors cite data that 10-30% of childhood HS occur as a result of both hereditary hemophilia and von Willebrand disease, thrombocytopenia, liver dysfunction, vitamin K deficiency.[57–59] In a study by Sharma S., et al, Yilmaz C., et al, the most common risk factors for HS were blood clotting disorders associated with vitamin K deficiency.[60,61]

Lo W.D., et al, Al-Jarallah A., et al, revealed genetic or acquired hemostasis defects in HS in children in 9% and thrombocytopenia in 6% of cases.[31,62]

Acquired coagulation disorders in children provoke liver and kidney diseases, including nephrotic syndrome with loss of coagulation factors.[63]

The direction of hemostatic disorders in HS was represented by hypocoagulation in about 10% of cases.[28]

Cerebral Venous Vessel Thrombosis and Hemorrhagic Stroke in Children

The incidence of venous vascular thrombosis (CSVT) of the brain in children averages 0.29 - 0.67 per 100 000 children per year.[64,65] In the neonatal period, CSVT is 2.6 per 100 000 children per year.[65,66] The mortality rate for CSVT in children is 6 - 30%.[67,68]

Risk factors for CSVT in newborns are acute conditions associated with the perinatal period: asphyxia during childbirth, generalized infection, dehydration, and the tendency of newborns to thrombosis.[64,69]

In older children, significant CSVT factors are injury to the dural sinuses during intracranial surgery or traumatic brain injury, taking oral contraceptives, glucocorticosteroids, protein S deficiency, anemia, connective tissue pathology, liver failure, nephropathy, malignant neoplasms, septic conditions or local infection in the head and neck,[64,70–76] prothrombotic disorders.[64,77,78]

CSVT determines thrombosis in cerebral veins, superficial or deep venous sinuses, obstruction of blood flow, venous stasis, impaired transport of cerebrospinal fluid.[64,66,73,79]

The frequency of HS in CSVT has maximum values: 6.5 - 25.0 per 100 000 children per year.[80–82]

In newborns, CSVT is a common cause of intraventricular hemorrhages.[65,83] To a lesser extent, CSVT causes primary subdural and subarachnoid hemorrhage.[73,84]

Infections and Hemorrhagic Stroke in Children

Up to a third of HS cases in children occur in the context of infection.[85]

Of 104 Saudi children with HS, infectious and inflammatory diseases were identified as a risk factor in 18 (17.3%) children.[86] Observations by Lo W.D, et al, showed that infection of the central nervous system, including as a component of systemic disease, was the cause of the development of HS in 9% of cases.[62] Cases of childhood HS have been reported with microbial associations such as chlamydia, enterovirus, parvovirus 19, influenza A virus, coxsackie, mycoplasma.[87–89]

The spectrum of infection in HS also includes bacterial meningitis, Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus, systemic lupus erythematosus, neurobrucellosis, as well as congenital toxoplasmosis and congenital rubella syndrome.[90,91] There are studies that have shown that the persistence of herpes viruses, Cytomegalovirus, Epstein-Barr virus, as well as bacterial, tuberculous meningitis and HIV infection can serve as risk factors for HS.[64,92–95] In HIV infection, hemorrhage was accompanied by secondary HIV - induced vasculitis, vasculopathy, thrombocytopenia or coagulopathy.[96]

Hemorrhagic complications in the presence of an infectious agent are triggered by a systemic inflammatory process, endothelial dysfunction, which, when combined with prothrombotic activity, leads to damage to the vascular wall, vasculopathy, thrombosis, occlusion of the vessel lumen.[86,97–99]

Vasculitis and Hemorrhagic Stroke in Children

Cerebral vasculitis (CV) is more common in children over the age of 14 and can be of primary or secondary, as well as infectious and non-infectious etiology.[100,101]

In primary vasculitis there are no diseases of organs and systems with concomitant inflammation of blood vessels.[102,103]

Secondary CNS vasculitis occurs in systemic lupus erythematosus, Schenlein-Genoch purpura, polyarteritis nodosa, Takayasu arteritis, Wegener's granulomatosis, Kawasaki disease, malignant neoplasms.[104–109]

In all cases of HS (average 4.6%) vasculitis, it provokes inflammation, damage and dysfunction of the vascular wall endothelium, lymphocytic, transmural infiltration from T - and other inflammatory cells, thrombosis.[102,103]

Cardiovascular Diseases and Hemorrhagic Stroke in Children

Cardiovascular diseases increase the risk of developing HS (2.6 - 6.8%) in children. Among cardiovascular diseases, congenital and acquired heart defects can lead to the development of HS in children. The development of HS in heart defects is mainly associated with intracardiac bypass surgery from right to left in most defects.[110–112] HS in children can develop in the early stages after surgical, invasive heart interventions, in pediatric cardiac surgery patients on extracorporeal membrane oxygenation.[113–120] Acquired heart diseases (endo and myocarditis, cardiac arrhythmias, cardiomyopathy, rheumocarditis) are also classified as a risk factor for HS in children.[118]

In childhood, HS occurs less frequently against the background of arterial hypertension (0.3 - 2.2% of cases).[121–124]

However, in the observations of Al-Jarallah A., et al, there was no association of HS with systemic hypertension in children.[31]

Oncological Diseases and Hemorrhagic Stroke in Children

HS is a known complication in patients with malignant oncological diseases.[62,123]

Lo W.D., et al, in a 7-year retrospective analysis of 85 children with non-traumatic intracranial hemorrhage, brain tumors were found in 15% of cases, Al-Jarallah A., et al - in 13.2%.[31,62]

However, other studies show a lower probability of developing HS in children with cancer (0.55 - 4%).[125–129]

Bowers D.C., et al, calculated the time interval for the development of HS in brain tumor survivors, which averaged 9.8 years after diagnosis of leukemia, and an average of 13.9 years since diagnosis of cancer.[130]

Zadeh C., et al, revealed HS in 40% of children with leukemia, Kyrnetskiy E.E., et al, in 30 children with brain tumors, in 19 children with acute leukemia and 2 children with lymphoma.[131,132] In studies by Noje C., et al, the prevalence of HS in children with acute lymphoblastic leukemia (ALL) was 2.6%, with acute myeloblastic leukemia (AML) - 3.3%, with various types of lymphoma - 1.6%.[129] Di Mario F.J., et al, identified HS with the same distribution between ALL, AML and lymphoma.[133] In the observations of Packer R.J., et al, HS was found in 4% of children with ALL, 13% with AML, 1% with lymphoma, 6% with neuroblastoma, 5% with bone tumor and 1% with other tumors.[125]

Most HS occurred in the early stages of cancer treatment. It was found that a dose of radiation to the skull of more than 50 Gray increased the risk of death from cerebrovascular disease by 17.8 times.[134,135] HS was caused by a combination in the treatment of L-asparaginase, prednisone, radiation and chemotherapy.[104,131,136–139]

Modifiable risk factors for the development of HS in patients with leukemia and lymphoma include hypercoagulation and hyperviscosity.[130,140] Many authors claim that vasculopathy, which occurs after several months or years with various tumors, as well as after radiation therapy, can lead to the development of HS.[87,141–143]

Genetic Polymorphisms, Hereditary Diseases in the Development of Hemorrhagic Stroke in Children

Sickle Cell Anemia. Sickle cell anemia (SCD) is a hereditary hemoglobinopathy, which is manifested by the production of abnormal hemoglobin S, a change in the shape and properties of red blood cells. HS in SCD occurs with a frequency of 17 - 44 per 100 000 people.[144–147] Mortality in the first 2 weeks after HS in SCD is 26%, recurrence of HS is 6.4 cases per 100 000 with an average time to recurrence of 7.2 months.[148]

Factors that can lead to cerebrovascular damage in SCD include low hemoglobin concentration, chronic anemia, low oxygen content in the blood, which leads to impaired cerebral blood flow. Other factors include a high white blood cell count, as well as SCD treatment measures: blood transfusion within the last 14 days, treatment with corticosteroids and nonsteroidal anti-inflammatory drugs.[148] In patients with SCD and stroke, blood clots, accumulation of sickle-shaped erythrocytes and other cells, damage to the endothelium, hyperplasia of the internal elastic membrane, scarring of the media, abnormal blood flow rate, formation of aneurysms, more often in the vertebrobasilar system, were also observed in the affected large arteries.[149–152]

Moyamoya Disease or Syndrome. Moyamoya disease or syndrome is a non-atherosclerotic, non-inflammatory, non-amyloid vasculopathy characterized by progressive stenosis of the distal intracranial sections of the internal carotid artery, less often the proximal sections of the anterior, middle, posterior and basilar arteries with the development of basal collateral vessels.[153] Genetic polymorphism of HLA class II genes is associated with Moyamoya disease. Moyamoya syndrome is also known, which occurs against the background of associated pathology: SCD, Down syndrome, neurofibromatosis, previous irradiation of the skull.[154,155] MMD occurs with a frequency of 0.086 per 100 000 children, in the first decade of life, more often in girls.[38,156,157] Most patients with MMD have subarachnoid hemorrhages. The clinical course in 20% of cases of the disease may manifest HS with progressive neurological disorders, hemiplegia, seizures, mental retardation and motor deficits.[38,158–161]

Hyperhomocysteinemia. Hyperhomocysteinemia (Hyper-Hcy) is a genetically determined, hereditary metabolic defect, the primary link of which is a violation of the metabolism of sulfur-containing amino acids. The cause of Hyper-Hcy may be a deficiency of cystathionine β - synthetase, homocysteine methyltransferase, as well as a mutation of the methylenetetrahydrofolate reductase (MTHFR) gene involved in homocysteine metabolism (polymorphism A1298C of the MTHFR gene). MTHFR is also a key enzyme in folic acid metabolism in vivo.[162,163]

Hyper-Hcy may cause a deficiency of folic acid or vitamin B_2, B_{12}.[2] The mechanism of cerebrovascular disease in Hiper-Hpu is hypercoagulation, hyperaggregation of platelets, which leads to thrombosis, especially of the carotid arteries, arterial dissection, vascular endothelium damage, neurotoxic effect.[21,164–166] A number of studies have shown an association of HS with elevated cholesterol levels in the blood. At the same time, the risk of ICH increases.[167,168]

Antiphospholipid Syndrome. Antiphospholipid syndrome (APS) is a systemic autoimmune disease with a high titer to phospholipids (PL) of antibodies such as antibodies to cardiolipin, antibodies to lupus anticoagulant and antibodies to cofactor proteins (prothrombin, protein C, protein S, annexin V,

prostacyclin and beta2-glycoprotein-I (beta2-GP-I).[169] The main consequence of APS, which can provoke HS, are arterial or venous thrombosis of various localization.[68,170,171] Ferro J.M., et al, found antiphospholipid antibodies in 22.6% of patients with CSVT, Martinelli I, et al, in 9 patients out of 121 examined patients with CSVT.[68,172] The most common forms of APS are primary and secondary APS. In childhood, secondary APS is more often observed, which develops when taking medications (psychotropic, hormonal, contraceptive, novocainamide, interferon alpha in high doses), viral and bacterial infections, autoimmune diseases, as well as malignant neoplasms.[170,173]

HS with neurological symptoms is observed in about 20% of patients.[174]

The risk of developing HS is associated with such a genetic pathology as a mutation of collagen formation, which determines defects in the structure of blood vessels.[28]

HS may also develop against the background of arteriopathy associated with heterozygous mutations in the CTSA gene.[175]

Metabolic Hemorrhagic Stroke in Children

Some authors distinguish "metabolic stroke" (MS) as a consequence of a metabolic disorder of an innate or acquired nature.[176]

Congenital metabolic disorders determine Handy - Schueller - Christchen disease, deficiency of biotin, nicotinic acid, vitamins B, C, Fabry disease and others. MS can complicate the course of certain mitochondrial diseases and syndromes: Mytochondrial Encephalopathy, Myepathy, Lactatacidosis, Stroke like episodes (MELAS), Pearson-Murrow syndrome and others. In these conditions, there are diseases of internal organs and concomitant metabolic disorders. The main biochemical sign of the entire mitochondrial pathology is lactate acidosis, an increase in the level of lactic and pyruvic acids in the blood and liquor, aciduria. Violations of local fibrinolysis, vasculopathy, angiopathy are observed, which determines both transient and persistent disorders of cerebral circulation.[177–179]

MS is observed as a consequence of acquired somatic diseases in children with severe diabetes mellitus, chronic liver and pancreatic diseases, after undergoing severe intestinal surgery, anesthesia, uncompensated alkalosis or acidosis.[64,92,180] Pappachan J., et al, describe the clinical signs of MS: persistent vomiting, hypo or hyperglycemia, organic acidemia, urea cycle disorders, mitochondrial disorders.[49]

Burdened Perinatal History as a Risk Factor for Hemorrhagic Stroke in Children

Shirokostyuk L. A. points out that 63% of children with cerebrovascular pathology have equal proportions of maternal diseases, unfavorable course of pregnancy and childbirth in the mother, difficulties of adaptation in the neonatal period.[181] An important role in the occurrence of HS was played by intranatal factors: signs of uteroplacental insufficiency, fetal distress, rupture of the membranes, early discharge of amniotic fluid, contaminated water, severe infections, childbirth using instruments (forceps or vacuum aid), emergency cesarean section, prematurity and postponement, an Apgar score of less than 7 points, intensive care at birth, hypoglycemia, congenital heart disease.[4,91,182–187]

Drug Use

Mainly in the adolescent population, it is not uncommon to develop hemorrhages due to taking drugs such as amphetamines, ecstasy, cocaine, phencyclidine, sniffing glue.[188,189]

Unknown Risk Factors for Hemorrhagic Stroke in Children

Unknown HS risk factors in children after a thorough diagnostic search, according to Malik A.A., et al, account for 30% of cases.[57]

Cohort studies by Beslow L.A., et al, Jordan L.C., et al, showed an unknown etiology of childhood strokes in 9-23% of cases, Lanthier S., et al, DeVeber G., et al in 10-15%, Chung B., et al - 12%.[16,28,29,64,123]

Median frequency of HS risk factors in children are shown in Diagram 1.

Neurological Manifestations of Hemorrhagic Stroke in Children

In older children, the main signs of HS are: headache, vomiting, difficulty speaking, visual deficits, coordination disorders, changes in consciousness, hemi and tetraplegia, seizures.[13,15,16,25,31,33,34,190,191] Beslow L.A., et al, observed acute symptomatic seizures in intracranial hemorrhage in 36% of patients.[192] Fox S., et al, revealed that intracranial hypertension and cerebral edema rapidly progress after HS.[191]

The younger the child, the more nonspecific the initial clinical features of HS may be.[13] Thus, seizures are considered to be common initial manifestations of HS in young children.[64,192,193] Lo W.D. believes that in children under 6 years of age, the most common signs of HS include both seizures and changes in mental status, vomiting, respiratory distress, lethargy, weakness. Young children do not report headaches.[13] Meyer-Heim A., et al, Calder K., et al, pointed to more diverse manifestations of the acute period of HS, when along with irritability or drowsiness there were problems associated with feeding the baby, vomiting and symptoms of peripheral hemodynamic disorders, a bulging large fontanel.[32,194]

Certain types of stroke are characterized by different clinical manifestations. Thus, SAH can manifest itself by sudden onset, headache, irritability, photophobia, loss of vision, inability to move limbs, difficulty speaking, loss of consciousness, periodic seizures and meningeal syndrome.

With IVH, unconsciousness, respiratory rhythm disturbances with hypoventilation, apnea, generalized tonic seizures

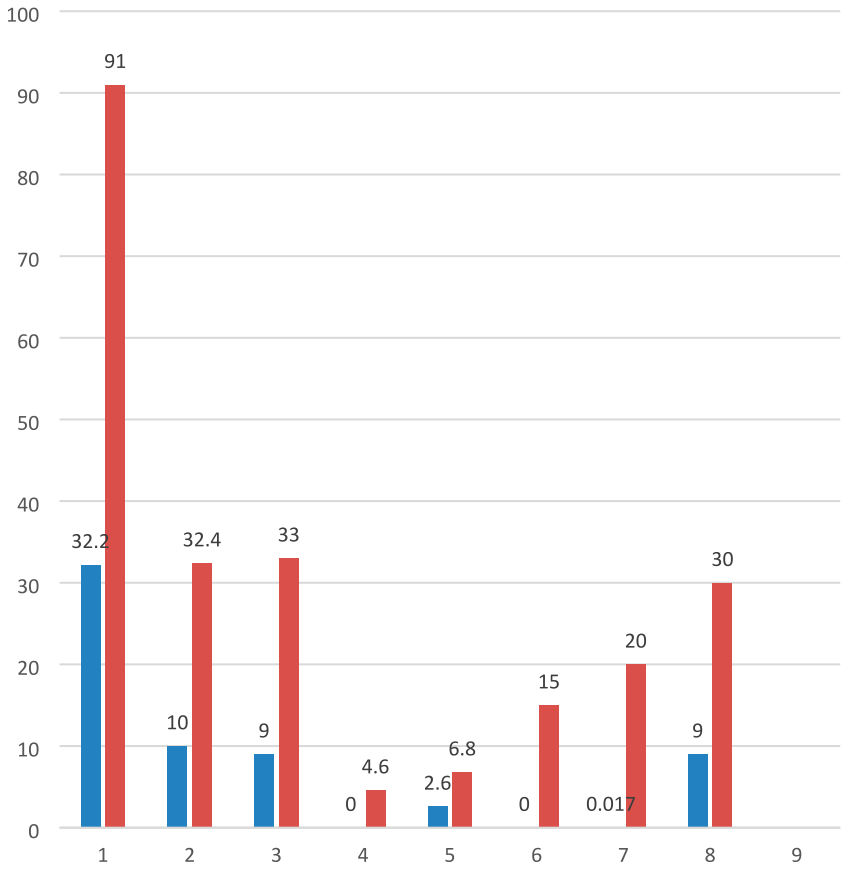

Diagram 1. Median frequency of HS risk factors in children. Row 1 - cerebrovascular pathology (32,2 - 91%), row 2 - hemostasis disorders (10 - 3.4%), row 3 - infections (9 - 33%), row 4 - vasculitis (0 - 4.6%), row 5 - cardiovascular diseases (2.6- 6.8%), row 6 - oncological diseases (0 - 15%), row 7 - genetic polymorphisms, hereditary diseases (0 - 20%), row 8 - unknown (9 - 30%).

or decerebral rigidity, bradycardia, arterial hypotension, fontanel bulging, tetraparesis, and schizophrenia are more common.[195]

With intracerebellar hemorrhages revealed symptoms of compression of the brain stem: bradycardia, apnea, increased intracranial pressure with swelling of the fontanel, divergence of the sutures of the skull, moderate dilation of the ventricles, as well as paresis of facial muscles, tetraparesis, opisthotonus. Subdural hemorrhage shows signs of compression of the brain stem: anisocoria with no photoreaction of the pupils, sopor or coma, as well as rigidity of the occipital muscles, opisthotonus and bradycardia.[33,196]

Bulbar dysfunction and dysarthria indicate involvement of the brain stem, while aphasia suggests involvement of the basal ganglia, thalamus, or hemispheres of the brain.[197]

In children with spontaneous ICH, headache, loss of consciousness and vomiting were common symptoms upon admission.[39]

Therapeutic Measures for Hemorrhagic Stroke in Children

HS in childhood in most cases requires urgent neurosurgical care. In this regard, at the beginning of HS therapy, a neurosurgeon's conclusion on the need for neurosurgical intervention is necessary. The presence of indications for surgical intervention dictates the interaction of the neurosurgeon with the anesthesiological teams. Currently, the possibilities of an augmented reality (AR) system are being considered - projecting three-dimensional images of the anatomy of the brain or spinal cord onto realistic models of patients, which helps in neuronavigation and surgical planning.[198]

The polyethologicity of HS in childhood often requires a multidisciplinary approach to identify the root cause of HS, which determines further HS therapy in children. HS treatment methods determine the need for patients to stay in the intensive care unit, in conditions of monitoring vital signs (pulse, blood pressure, respiratory rate, saturation, etc.). Emergency therapy is: maintenance of respiratory, cardiac activity, blood pressure, oxygenation, water-salt metabolism, treatment of cerebral edema, glucocorticosteroid therapy, optimization of glycemia, prevention and correction of hyperthermia, infections.[6,38,199]

Restoration of Respiration and Gas Exchange in Children with Hemorrhagic Stroke

Restoration of respiration, patency of the respiratory tract, gas exchange is required by patients with impaired consciousness (sopor, coma), respiratory rhythm (for example, apnea), loss of protective reflexes of the respiratory tract (cough and vomiting),

as well as in the presence of known clinical signs of respiratory insufficiency: cyanosis, indicators of partial oxygen tension in arterial blood (PaO_2): 50 - 79 mmHg, carbon dioxide ($PaCO_2$): 45 - > 70 mmHg, arterial oxygen saturation (SaO2): 94 - 75%. In the limit values of these indicators, as well as in case of cardiorespiratory destabilization, patients should be intubated and transferred to artificial lung ventilation (ALV).[200,201]

Stabilization of Hemodynamics in Hemorrhagic Stroke in Children

Stabilization of hemodynamics in children with HS primarily involves the management of blood pressure (BP), since an increase in blood pressure in children with HS can lead to continued or repeated bleeding, impaired cerebral perfusion.[202–204] However, there are no recommendations for specific target ranges of blood pressure in children.[38,205] Fujimura M., et al, suggest reducing high blood pressure by 15-25% during the first 24 hours, with a gradual decrease in the future.[206] Rivkin M.J., et al, recommend the treatment of blood pressure in children when it exceeds normal values by 15% for more than an hour or at any time when blood pressure exceeds 20%.[207] Vasospasm is treated with hemodilution to improve perfusion, calcium channel antagonists, in particular nimodipine, as well as antihypertensive drugs, beta blockers, possibly ACE inhibitors.[49,204,208] However, the question of the effectiveness of these drugs remains open.[209]

Infusion Therapy for Hemorrhagic Stroke in Children

Infusion therapy for HS in children is necessary to maintain euvolemia, perfusion pressure, and regulation of intracranial pressure (ICP). Intravenous access is necessary for this purpose. However, the permissible amounts of infusion therapy for HS in children require clarification. Thyagarajan B., in the absence of contraindications, some infusions are recommended to be administered in the volume of enteral nutrition. In infancy, the optimal nutritional substrate is breast milk. In case of impaired swallowing function, as well as in patients who are in a state of somnolence or coma, due to the high risk of aspiration, it is necessary to install a gastric probe.[210]

There is insufficient research on the qualitative composition of infusion therapy for HS in children. Lo W., in children with HS, recommends the use of saline solutions of liquids, since hypotonic solutions contribute to the development of cerebral edema.[13]

The use of hypertensive solutions for infusions in patients with HS effectively reduced intracranial pressure.[211] A combination of crystalloid solutions with hydroxyethyl starch-based colloids is acceptable for HS.[212]

When the hemoglobin (Hb) level is < 5 g/dl, hemotransfusion is required at the rate of 10 mL / kg. The hemoglobin level should be maintained at 100 g/l. This provision is consistent with the recommendations of the World Health Organization (WHO).[38]

Treatment of Cerebral Edema, High Intracranial Pressure in Hemorrhagic Stroke in Children

After HS, neurological deterioration may progress for several days. One of the main causes of this is cerebral edema, increased ICP and secondary brain damage.[213,214] So, in a study by Gebel J.M., et al, with IPH, the absolute volume of edema doubled in the first 24 h after treatment.[215]

In childhood, intensive therapy of elevated ICP in HS is required, since children do not have cerebral atrophy of aging, which gives space to accommodate the mass effect.[191] In order to reduce sharply increased intracranial pressure, intracerebral hematomas must be removed, but it is not clear whether this leads to improved outcomes.[38] Beslow L.A., et al, propose to install an intraventricular catheter (IVC) for therapeutic as well as diagnostic purposes in some cases of pediatric HS. IVC will allow both drainage of cerebrospinal fluid and measurement of ICP.[29] Non–surgical methods for reducing elevated ICP include holding the headboard of the patient's bed at an angle of 30°, which promotes venous drainage of the brain, as well as hyperventilation to pCO2 - 25-30 mmHg and reducing blood volume by stimulating osmotic diuresis. Hyperosmolar therapy with mannitol or hypertonic solution, as well as sedation, is recommended for this.[6,215] Mannitol is not suitable for use when the osmotic plasma pressure is >320 mOsm, since high osmotic plasma pressure leads to dehydration, but mannitol can increase the osmotic pressure of the hematoma and change the osmotic pressure gradient.[216–218]

Alternatives to mannitol may be a hypertonic solution, which has a longer effect and does not violate the BBB, as well as furosemide.[219]

Furosemide is allowed to be combined with mannitol or hypertonic solution.[220,221]

Glucocorticosteroid Therapy for Hemorrhagic Stroke in Children

Some authors believe that in conditions of severe stress effects in HS in children, including those caused by surgery under general anesthesia, replacement glucocorticosteroid therapy (GCS) is necessary.[222–224]

Lo W. it recommends the use of GCS for vasogenic edema of the brain.[13]

However, hyperglycemia, suppression of the function of the hypothalamic-pituitary-adrenal system, infectious complications and diabetes are harmful as a result of the use of GCS.[225,226]

Treatment of Hemostasis in Hemorrhagic Stroke in Children

Recommendations for the management of hemostasis in HS in children require compensation for deficient blood clotting factors.[227] Thus, patients who have serious thrombocytopenia of

non-immunological origin should be transfused platelet mass. Routine platelet transfusion is performed with a platelet count of less than 50 × 109 / L.[228,229] Vitamin K-dependent HS should be prescribed vitamin K. To increase the level of coagulation factors, a prothrombin complex concentrate or freshly frozen plasma can also be used, which simultaneously reduces the risk of hematoma enlargement. However, the authors remind that these hemostatic measures pose a risk of thromboembolism.[13] To reduce the volume of bleeding and stabilize hematomas in children during the first 4 hours after HS, the use of recombinant factor VIIa is recommended.[230,231]

There is also a benefit from hematoma lysis with thrombolytics in cases of early treatment of HS.[232,233] At the same time, some authors have identified the conversion of ischemic stroke to hemorrhagic stroke both naturally and with the introduction of a tissue plasminogen activator.[234] Thus, the effect of anticoagulants, thrombolytics on acute HS in children requires systematic study.[2]

Treatment of Seizures in Hemorrhagic Stroke in Children

Al-Jarallah A., et al, found that seizures complicate childhood stroke in 10.3% of cases, Jordan L.C., et al, in 20%.[31,193] Recurrent seizures increase the risk of recurrent hemorrhages, exacerbate brain damage and lead to negative long-term results.[235] In this regard, in clinical seizures, as well as convulsive activity, including those detected during EEG, treatment of this condition is required.[38,236] Ferriero D.M., et al, recommend prescribing anticonvulsants for a short period of time after HS.[6] The first-line drug for the treatment of seizures is Phenobarbital, Phenytoin, the second line is Lidocaine, the third line is Midazolam, Levetiracetam, Clonazepam, Lorazepam.[237–247]

However, many authors note that there are no studies on the safety, efficacy, and specificity of the use of anticonvulsants in HS in various periods of childhood.[38,215,248]

Neuroprotection in Hemorrhagic Stroke in Children

Neuroprotection involves protecting the brain from secondary damage and degeneration in HS. Neuroprotective therapy includes medications, most of which are currently in clinical trials.[249]

Relative neuroprotective properties are citicoline derivative, Edaravone, Erythropoietin, NeuroAid (MCLC601), Actovegin, magnesium sulfate (MgSO4), hypothermia. However, for the treatment of HS in children, these drugs need additional multicenter, randomized clinical trials, since the effectiveness of these neuroprotective agents was analyzed in ischemic stroke, in experimental animal studies, or the neuroprotective properties of these drugs had contradictory results.

If a child who has had HS has a treatable risk factor for stroke, the underlying disease should be treated.[38] There are recommendations for the treatment of some probable risk factors HS. For example, microsurgical and endovascular treatment methods are used in children with AVM, KA.[47,250]

It is useful to add folic acid, vitamin B_6 and B_{12} to the treatment of hyperhomocysteinemia, along with weight control and diet changes. Children with SCD are recommended to receive blood transfusion for a long time for primary and secondary prevention of stroke, until a decrease in sickle cell hemoglobin <20-30% with hematocrit >30%.[251,252] It is also recommended to administer hydroxyurea, hematopoietic stem cell transplantation, gene therapy, direct and indirect revascularization.[253–255]

Supportive treatment for CSVT should include adequate hydration, control of seizures, treatment of increased intracranial pressure, and thrombolytic therapy.[38]

Calcium channel blockers, aspirin, and surgical revascularization methods are recommended for the treatment of MMD.[159]

The Outcome of Hemorrhagic Stroke in Children

The average risk of recurrent HS in children is 20-35%. In children with one identified HS risk factor, the probability of recurrent HS is within 8%, with a combination of two or more factors, the recurrence of HS is 42%.[28,256–258] Children with hematological disorders, vascular malformations, and tumors had a high risk of recurrence.[28,32,259] In children with medical etiology (for example, thrombocytopenia, hypertension), the 5-year cumulative recurrence rate was 13%. However, there were no relapses in children with idiopathic HS.[37]

Neurological Outcome in Hemorrhagic Stroke in Children

Long-term neurological deficit after HS was found in 45-50% of children.[62,258] Two years after perinatal HS, moderate or severe deficiency was detected in 5% of children.[185]

The nature of neurological complications after HS in older children was determined by hemiparesis in 25.0% of cases, aphasia (7.4%), epileptic seizures (10.3%), hydrocephalus (4.4%).[31] In the observations of Chang B., et al, of the 14 patients with HS, 41% of the survivors had long-term neurological disorders, including mental retardation (N = 11), epilepsy (N = 7) and hemiplegia (N = 10). Seizures at initial admission were a significant risk factor for long-term neurological deficits.[16]

Blom I., et al, observed 36 patients after HS. Six children had epileptic seizures, 11 had hemiparesis of varying severity, 3 had symptoms of cerebellar ataxia, one child had persistent tetraparesis, and one had paraparesis. Signs of cognitive impairment were found in 15 patients. Most had low self-esteem, as well as emotional, behavioral, and health problems.[258] Some studies have revealed persistent neurological deficits in 65-66% of children who have had HS. Subsequently, problems with the development, education of children, as well as convulsive disorders developed.[28,34,256,260,261]

Other authors, in half of the children who suffered a HS, motor and cognitive impairments were subsequently observed.[14,19,62,159]

Table 3. Indicators of HS outcome in children.

AUTHOR, YEAR OF PUBLICATION	THE OUTCOME OF HS IN CHILDREN				
	RECURRENCE RATE (%)	AUTHOR, YEAR OF PUBLICATION	THE FREQUENCY OF NEUROLOGICAL DEFICITS (%)	AUTHOR, YEAR OF PUBLICATION	MORTALITY RATE
DeVeber G., 2005[257]	25	Porcari G.S., et al, 2020[185]	5	Chung B., et al, 2004[16]	0.34 per 100 000 children
Lynch J. K., et al, 2005[11]	33.3	May-Llanas M.E, et al, 1999[34]	35	Launthier S., et al, 2000,[28] Fullerton H.J., et al, 2002[264]	0.6 per 100 000 children
Launthier S., et al, 2000[28]	42	Chung B., et al, 2004[16]	41	Lynch J.K., et al, 2002[11]	2-3 cases per 100 000 children
		Lo W.D., et al, 2008,[62] Lanthier S., et al, 2000,[28] Al-Jarallah A., et al, 2000[31]	45 - 47	Al-Jarallah A., et al, 2000[31]	8.8%
		Blom I., et al, 2003,[258] Beslow L.A., et al, 2010[29]	50	Porcari G.S., et al, 2020[185]	12%
		DeVeber G., 2005,[265] Neuner B., et al, 2011	65 - 66	Blom I., et al, 2003,[258] Broderick J., et al, 1993,[8] Lin C.L., et al, 1999[39]	21 - 23%
				Meyer-Heim A. D., et al, 2003,[32] Lynch J.K., et al, 2005[11]	25%
				Lo W.D., et al, 2008, 2013,[62,124]	34.11%
				May-Llanas M.E., et al, 1999,[34] Eeg-Olofsson O., et al, 1983[15]	36 - 38%
				Livingston J.H., et al, 1986[33]	54%

Beslow L.A., et al, after examining 26 patients with ICH, clarified that motor disorders were observed in 38% of survivors, and cognitive disorders in 50%.[29] During long-term follow-up of 42 children with spontaneous ICH, 3% of children retained visual deficits, speech delay within 25 - 36%.[39,182] However, Bruno C.J., et al, argue that 1 year after perinatal HS, moderate or severe deficits are observed in few children.[262]

There are studies that have studied the factors accompanying the adverse neurological outcome of HS in children. Thus, a more severe outcome of HS was observed in newborns and children <3 years old, as well as in the presence of aneurysms, hematological disorders, infratentorial hemorrhage location, a score on the Glasgow coma scale (SCG) at admission ≤ 7, a change in mental status within 6 hours after hospitalization.[32,54] At the same time, Lo W.D. did not find a positive correlation between the initial Glasgow coma scale, the localization of bleeding and the outcome of HS.[13]

The ratio of intracerebral hemorrhage volume to total brain volume was also important for HS outcomes: the volume of hemorrhage, which is 2% of the total brain volume, leads to moderate disability, 4% to severe disability.[123,263] In a prospective, single-center, cohort study of children with ICH, with an average follow-up period of 3 to 7.5 months, neurological disorders were detected in 71% of survivors in patients with a hemorrhage volume of more than 2% of the total brain volume. At the same time, 55% of children had significant disabilities.[29] A poor result after HS was observed with a combination of several risk factors.[28]

Mortality in Hemorrhagic Stroke in Children

Estimates of the annual mortality rate after HS in children vary in individual studies. Some authors claim that HS is among the top ten causes of death in childhood, which is 2-3 cases per 100 000 children.[11] Other authors give a mortality parameter of 0.6 cases per 100 000 children per year.[28,264] Chung B., et al, determined that this indicator is 0.34 cases per 100 000 children.[16]

In studies by Livingston J.H., et al the mortality rate was 54%.[33] For other authors, this indicator ranged from 5 to 38%.[8,15,29,31,32,34,39,62,159,185,257,265,266] Some studies are devoted to identifying factors that predict mortality after HS in children. Thus, the risk of death is significantly increased with repeated episodes of HS (by 40%) than with a single episode of HS (16%), as well as with ICH located in the brain stem, cerebellum and several subcortical areas (33%), among boys, children of the black race, in patients with GCS 3 - 5.[28,39,62,257,263] Adil M.M., et al, revealed the greatest association with mortality in patients with coma and coagulopathy.[267] However, a number of studies indicate a significant decrease in mortality after HS in children over the past 2 decades. This statement applies primarily to IPH (58% reduction in mortality), as well as to SAH (79-50% reduction in mortality), which is associated with improved pediatric intensive care and neurosurgical care.[263,268,269] The outcome indicators of HS in children are presented in Table 3.

Conclusion

Thus, an analysis of current knowledge about HS in childhood shows the variable nature of the results. This applies primarily to epidemiology, outcomes, as well as the cause of HS development in children. However, the information presented presents childhood HS as a common pathology that has a tendency to relapse, determines early disability and a high incidence of deaths. ICH is more often registered, then SAH. Information about other types of HS specified in the ICD 11 edition is limited in children. HS affects boys more often than girls. The causes of this phenomenon are unknown. HS is more common in children under 2 years of age.

Determination of the etiology, assessment of risk factors for HS in children is an area that requires systematic study with the formation of high-risk groups for the development of HS in children. This is explained by the fact that the nosologies that determine HS in children include numerous intra and extracerebral causes. Cerebrovascular pathology occupies a leading position in the spectrum of nosologies. Obvious risk factors for HS in children include impaired coagulating and anticoagulating properties of blood, cardiovascular, oncological diseases, and infections. The likely target group for HS development is children with CSVT, vasculitis. The state of health of the child's parents, obstetric history, perinatal factors are important, especially in the implementation of perinatal HS. Rare genetic, hereditary diseases appear, in the structure of which HS can develop in children.

The multifactorial nature of HS in childhood determines the variety of clinical manifestations, which requires a timely differentiated, multidisciplinary approach to the diagnosis of HS.

It is necessary to search for the best strategies for providing neurointensive care to children in the acute period of HS, based on multicenter, randomized clinical trials and a convincing evidence base in accordance with the type of HS, age of children, predictors of the disease.

Instructions are required to optimize the respiratory function in HS in children with its violation, which include a list of indications for tracheal intubation, timing of connection to a ventilator, setting parameters and modes of ventilation, procedures for stopping ventilation. Infusion therapy is important in HS in children, which allows to maintain homeostasis, nutrition of the body, administration medicines, especially in conditions of restriction of oral administration of fluids, electrolytes, nutrition in seriously ill patients. However, there are no clear guidelines for determining the daily fluid requirement in children at different age periods, volume, quality of enteral nutrition, composition of infusion media in HS. The latter is especially important, given the cerebral edema, increased intracranial pressure accompanying HS.

Recommendations for the management of hemostasis in children with HS require clarification, in accordance with the direction of hemostatic disorders. There are few therapeutic possibilities for effective neuroprotection, symptomatic therapy of HS in children.

Author Contributions

Contribution of the author **Askarova A.E.:** conceptualization; research; writing — initial version; review & editing

Zhurkabayeva B.D.: conceptualization; writing — review & editing.

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REFERENCES

1. Sébire G, Fullerton H, Riou E, deVeber G. Toward the definition of cerebral arteriopathies of childhood. *Curr Opin Pediatr*. 2004;16(6):617-622. doi:10.1097/01.mop.0000144441.29899.20
2. Carvalho KS, Garg BP. Arterial strokes in children. *Neurol Clin*. 2002;20(4):1079-1100. doi:10.1016/S0733-8619(02)00012-9
3. Thorvaldsen P, Asplund K, Kuulusmaa K, Rajakangas AM, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA project. World health organization monitoring trends and determinants in cardiovascular disease. *Stroke*. 1995;26(3):361-367. doi:10.1161/01.str.26.3.361
4. Armstrong-Wells J, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Prevalence and predictors of perinatal hemorrhagic stroke: results from the kaiser pediatric stroke study. *Pediatrics*. 2009;123(3):823-828. doi:10.1542/peds.2008-0874
5. Lynch JK. Epidemiology and classification of perinatal stroke. *Semin Fetal Neonatal Med*. 2009;14(5):245-249. doi:10.1016/j.siny.2009.07.001
6. Ferriero DM, Fullerton HJ, Bernard TJ, et al. Management of stroke in neonates and children: a scientific statement from the American heart association/American stroke association. *Stroke*. 2019;50(3):51-96. doi:10.1161/STR.0000000000000183
7. Jordan LC. Assessment and treatment of stroke in children. *Curr Treat Options Neurol*. 2008;10(6):399-409. doi:10.1007/s11940-008-0042-9
8. Broderick J, Talbot GT, Prenger E, Brott T. Stroke in children within a major metropolitan area: the surprising importance of intra-cerebral hemorrhage. *J Child Neurol*. 1993;8(3):250-255. doi:10.1177/088307389300800308
9. Giroud M, Lemesle M, Gouyon JB, Nivelon JL, Milan C, Dumas R. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993. *J Clin Epidemiol*. 1995;48(11):1343-1348. doi:10.1016/0895-4356(95)00039-9
10. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. *Neurology*. 2003;61(2):189-194. doi:10.1212/01.wnl.0000078894.79866.95
11. Lynch JK, Hirtz DG, DeVeber G, Nelson KB. Report of the ational nstitute of neurological disorders and stroke workshop on perinatal and childhood stroke. *Pediatrics*. 2002;109(1):116-123. doi:10.1542/peds.109.1.116

12. Lehman LL, Khoury JC, Taylor JM, et al. Pediatric stroke rates over 17 years: report from a population-based study. *J Child Neurol*. 2018;33(7):463-467. doi:10.1177/0883073818767039
13. Lo WD. Childhood hemorrhagic stroke: an important but understudied problem. *J Child Neurol*. 2011;26(9):1174-1185. doi:10.1177/0883073811408424
14. Zahuranec DB, Brown DL, Lisabeth LD, Morgenstern LB. Is it time for a large, collaborative study of pediatric stroke? *Stroke*. 2005;36(9):1825-1829. doi:10.1161/01.STR.0000177882.08802.3c
15. Eeg-Olofsson O, Ringheim Y. Stroke in children. Clinical characteristics and prognosis. *Acta Paediatr Scand*. 1983;72(3):391-395. doi:10.1111/j.1651-2227.1983.tb09734.x
16. Chung B, Wong V. Pediatric stroke among Hong Kong Chinese subjects. *Pediatrics*. 2004;114(2):206-212. doi:10.1542/peds.114.2.e206
17. Al-Sulaiman A, Bademost O, Ismail H, Magboll G. Stroke in Saudi children. *J Child Neurol*. 1999;14(5):295-298. doi:10.1177/088307389901400505
18. Kramarow E, Lentzner H, Rooks R, Weeks J, Saydah S. *Health and Aging Chartbook, Health, United States*. Hyattsville, MD: National Center for Health Statistics; 1999.
19. Laugesaar R, Kolk A, Tomberg T, et al. Acutely and retrospectively diagnosed perinatal stroke: a population based study. *Stroke*. 2007;38(8):2234-2240. doi:10.1161/strokeaha.107.483743
20. Carolei A, Marini C, Ferranti E. A prospective study of cerebral ischemia in the young: analysis of pathogenic determinants. *Stroke*. 1993;24(3):362-367. doi:10.1161/01.STR.24.3.362
21. Cardo E, Monros E, Colome C. Children with stroke: polymorphism of the MTHFR gene, mild hyperhomocysteinemia, and vitamin status. *J of Child Neurology*. 2000;15(5):295-298. doi:10.1177/088307380001500505
22. McKinney SM, Magruder JT, Abramo TJ. An update on pediatric stroke protocol. *Pediatr Emerg Care*. 2018;34(11):810-815. doi:10.1097/PEC.0000000000001653
23. Takenouchi T, Kasdorf E, Engel M, Grunebaum A, Perlman JM. Changing pattern of perinatal brain injury in term infants in recent years. *Pediatr Neurol*. 2012;46(2):106-110. doi:10.1016/j.pediatrneurol.2011.11.011
24. Cole L, Dewey D, Letourneau N. Clinical characteristics, risk factors, and outcomes associated with neonatal hemorrhagic stroke. *JAMA Pediatr*. 2017;171(3):230-238. doi:10.1001/jamapediatrics.2016.4151
25. Earley CJ, Kittner SJ, Feeser BR, et al. Stroke in children and sickle-cell disease: Baltimore-Washington cooperative young stroke study. *Neurology*. 1998;51(1):169-176. doi:10.1212/wnl.51.1.169
26. Jordan LC, Johnston SC, Wu YW, Sidney S, Fullerton HJ. The importance of cerebral aneurysms in childhood hemorrhagic stroke. *Stroke*. 2009;40(2):400-405. doi:10.1161/STROKEAHA.108.518761
27. Perkins E, Stephens J, Xiang H, Lo W. The cost of pediatric stroke acute care in the United States. *Stroke*. 2009;40(8):2820-2827. doi:10.1161/STROKEAHA.109.548156
28. Lanthier S, Carmant L, David M, Larbrisseau A, de Veber G. Stroke in children: the coexistence of multiple risk factors predicts poor outcome. *Neurology*. 2000;54(2):371-378. doi:10.1212/wnl.54.2.371
29. Beslow LA, Licht DJ, Smith SE, et al. Predictors of outcome in childhood intracerebral hemorrhage: a prospective consecutive cohort study. *Stroke*. 2010;41(2):313-318. doi:10.1161/STROKEAHA.109.568071
30. Cherry MG, Greenhalgh J, Osipenko L, Venkatachalam M, Boland A. The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation. *Health Technol Assess*. 2012;16(43):100-129. doi:10.3310/hta16430
31. Al-Jarallah A, Al-Rifai MT, Riela AR, Roach ES. Nontraumatic brain hemorrhage in children: etiology and presentation. *J Child Neurol*. 2000;15(5):284-289. doi:10.1177/088307380001500503
32. Meyer-Heim AD, Boltshauser E. Spontaneous intracranial haemorrhage in children: aetiology, presentation and outcome. *Brain Dev*. 2003;25(6):416-421. doi:10.1016/s0387-7604(03)00029-9
33. Livingston JH, Brown JK. Intracerebral haemorrhage after the neonatal period. *Arch Dis Child*. 1986;61(6):538-544. doi:10.1136/adc.61.6.538
34. May-Llanas ME, Alcover-Bloch E, Cambra-Lasaosa FJ, Campistol PJ, Palomeque Rico A. Non-traumatic cerebral hemorrhage in childhood: etiology, clinical manifestations and management. *An Esp Pediatr*. 1999;51(3):257-261.
35. Giroud M, Lemesle M, Madinier G, Manceau E, Osseby GV, Dumas R. Stroke in children under 16 years of age. Clinical and etiological difference with adults. *Acta Neurol Scand*. 1997;96(6):401-406. doi:10.1111/j.1600-0404.1997.tb00306.x
36. Boulouis G, Stricker S, Benichi S, et al. Etiology of intracerebral hemorrhage in children: cohort study, systematic review, ant meta - analysis. *J Neurosurg Pediatr*. 2021;27(3):357-363. doi:10.3171/2020.7.PEDS20447
37. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Recurrent hemorrhagic stroke in children: a population-based cohort study. *Stroke*. 2007;38(10):2658-2662. doi:10.1161/STROKEAHA.107.481895
38. Roach ES, Golomb MR, Adams R, et al. American heart association stroke ouncil; ouncil on cardiovascular disease in the young. management of stroke in infants and children: a scientific statement from a special writing group of the American heart association stroke ouncil and the ouncil on cardiovascular disease in the young. *Stroke*. 2008;39(9):2644-2691. doi:10.1161/STROKEAHA.108.189696
39. Lin CL, Loh JK, Kwan AL, Howng SL. Spontaneous intracerebral hemorrhage in children. *Kaohsiung J Med Sci*. 1999;15(3):146-151.
40. Krings T, Geibprasert S, TerBrugge K. Classification and endovascular management of pediatric cerebral vascular malformations. *Neurosurg Clin*. 2010;21(3):463-482. doi:10.1016/j.nec.2010.03.010
41. Carlin TM, Chanmugam A. Stroke in children. *Emerg Med Clin*. 2002;20(3):671-685. doi:10.1016/S0733-8627(02)00017-2
42. Plummer NW, Zawistowski JS, Marchuk DA. Genetics of cerebral cavernous malformations. *Curr Neurol Neurosci Rep*. 2005;5(5):391-396. doi:10.1007/s11910-005-0063-7
43. Gabriel RA, Kim H, Sidney S. Ten - year detection rate of braine arteriovenous malformations in a large, multiethnic, defined populations. *Stroke*. 2010;41(1):21-26. doi:10.1161/STROKEAHA.109.566018
44. Ding D, Starke RM, Kano H, et al. International multicenter cohort study of pediatric brain arteriovenous malformations, part 1: predictors of hemorrhagic presentation. *J Neurosurg Pediatr*. 2017;19(2):127-135. doi:10.3171/2016.9.PEDS16283
45. Hitchon P, Schneider PB. *Arteriovenous Malformations of the Brain. Neirobase: The Information Resource for Clinical Neurology*. Arbor Publishing Corp; 2005.
46. Huang J, McGirt MJ, Gailloud P, Tamargo RJ. Intracranial aneurysms in the pediatric population: case series and literature review. *Surg Neurol*. 2005;63(5):424-432. doi:10.1016/j.surneu.2004.11.023
47. Sanai N, Quinones-Hinojosa A, Gupta NM, et al. Pediatric intracranial aneurysms: durability of treatment following microsurgical and endovascular management. *J Neurosurg*. 2006;104(2Suppl):82-89. doi:10.3171/ped.2006.104.2.3
48. Krings T, Geibprasert S, TerBrugge KG. Pathomechanisms and treatment of pediatric aneurysms. *Child's Nerv Syst*. 2010;26(10):1309-1318. doi:10.1007/s00381-009-1054-9
49. Pappachan J, Kirkham FJ. Cerebrovascular disease and stroke. *Arch Dis Child*. 2008;93(10):890-898. doi:10.1136/adc.2008.142836
50. Chukhlovina ML, Guzeeva VM. Features of pathogenesis and diagnosis of a hemorrhagic stroke at persons of young age. *Clin Med*. 2004;3:11-15.
51. Young G, Manco-Johnson M, Gill JC, et al. Clinical manifestations of the prothrombin G20210A mutation in children: a pediatric coagulation consortium study. *J Thromb Haemostasis*. 2003;1(5):958-962. doi:10.1046/j.1538-7836.2003.00116.x
52. Zeller JA, Eschenfelder CH, Stingele R. Coagulation disorders and stroke Gerinnungsst orungen und schlaganfall. *Hämostaseologie*. 2006;26(4):309-315.
53. Abdullah WZ, Idris SZ, Bashkar S, Hassan R. Role of fibrinolytic markers in acute stroke. *Singapore Med J*. 2009;50(6):604-609.
54. Klinge J, Auberger K, Auerswald G, Brackmann HH, Mauz-Korholz C, Kreuz W. Prevalence and outcome of intracranial haemorrhage in haemophiliacs–a survey of the paediatric group of the German Society of Thrombosis and Haemostasis (GTH). *Eur J Pediatr*. 1999;158(Suppl 3):162-165. doi:10.1007/pl00014346
55. Revel-Vilk S, Golomb MR, Achonu C, et al. Effect of intracranial bleeds on the health and quality of life of boys with hemophilia. *J Pediatr*. 2004;144(4):490-495. doi:10.1016/j.jpeds.2003.12.016
56. Ries M, Wolfel D, Maier-Brandt B. Severe intracranial hemorrhage in a newborn infant with transplacental transfer of an acquired factor VIII: C inhibitor. *J Pediatr*. 1995;127(4):649-650. doi:10.1016/s0022-3476(95)70132-x
57. Mallick AA, O'Callaghan FJK. Risk factors and treatment outcomes of childhood stroke. *Expert Rev Neurother*. 2010;10(8):1331-1346. doi:10.1586/ern.10.106
58. Volpe JJ. Intracranial hemorrhage in early infancy: renewed importance of vitamin K deficiency. *Pediatr Neurol*. 2014;50(6):545-546. doi:10.1016/j.pediatrneurol.2014.02.017
59. Sukumar S, Lämmle B, Cataland S. Thrombotic thrombocytopenic purpura: athophysiology, diagnosis, and management. *J Clin Med*. 2021;10(3):536-543. doi:10.3390/jcm10030536
60. Sharma S, Suthar R, Dhawan SR, et al. Aetiological profile and short-term neurological outcome of haemorrhagic stroke in children. *J Trop Pediatr*. 2022;68(4):fmac040. doi:10.1093/tropej/fmac040
61. Yilmaz C, Yuca SA, Yilmaz N, Bektaş MS, Çaksen H. Intracranial hemorrhage due to vitamin K deficiency in infants: a clinical study. *Int J Neurosci*. 2009;119(12):2250-2256. doi:10.3109/00207450903170437
62. Lo WD, Lee J, Rusin J, Perkins E, Roach ES. Intracranial hemorrhage in children: an evolving spectrum. *Arch Neurol*. 2008;65(12):1629-1633. doi:10.1001/archneurol.2008.502
63. Schlegel N. Thromboembolic risks and complications in nephrotic children. *Semin Thromb Hemost*. 1997;23(3):271-280. doi:10.1055/s-2007-996100
64. DeVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. *N Engl J Med*. 2001;345(6):417-423. doi:10.1056/NEJM200108093450604
65. Ramenghi LA, Cardiello V, Rossi A. Neonatal cerebral sinovenous thrombosis. *Handb Clin Neurol*. 2019;162:267-280. doi:10.1016/B978-0-444-64029-1.00012-6
66. Heller C, Heinecke A, Junker R. Cerebral venous thrombosis in children: a multifactorial origin. *Circulation*. 2003;108(11):1362-1367. doi:10.1161/01.CIR.0000087598.05977.45

67. Mehraein S, Schmidtke K, Villringer A, Valdueza JM, Masuhr F. Heparin treatment in cerebral sinus and venous thrombosis: patients at risk of fatal outcome. *Cerebrovasc Dis*. 2003;15(1-2):17-21. doi:10.1159/000067117
68. Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the international study on cerebral vein and dural sinus thrombosis (ISCVT). *Stroke*. 2004;35(3):664-670. doi:10.1161/01.STR.0000117571.76197.26
69. Sorg A, Von Kries R, Klemme M, et al. Incidence and risk factors of cerebral sinovenous thrombosis in infants. *Dev Med Child Neurol*. 2021;63(6):697-704. doi:10.1111/dmcn.14816
70. Meena AK, Naidu KS, Murthy JMK. Cortical sinovenous thrombosis in a child with nephrotic syndrome and iron deficiency anaemia. *Neurol India*. 2000;48(3):292-294.
71. Milhaud D, Heroum C, Charif M, Saulnier P, Pages M, Blard JM. Dural puncture and corticotherapy as risks factors for cerebral venous sinus thrombosis. *Eur J Neurol*. 2000;7(1):123-124. doi:10.1046/j.1468-1331.2000.00003.x
72. Benedict SL, Bonkowsky JL, Thompson JA, et al. Cerebral sinovenous thrombosis in children: another reason to treat iron deficiency anemia. *J Child Neurol*. 2004;19(7):526-531. doi:10.1177/08830738040190070901
73. Sebire G, Tabarki B, Saunders DE, et al. Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. *Brain*. 2005;128(Pt 3):477-489. doi:10.1093/brain/awh412
74. Muthukumar N. Uncommon cause of sinus thrombosis following closed mild head injury in a child. *Child's Nerv Syst*. 2005;21(1):86-88. doi:10.1007/s00381-004-0926-2
75. Fluss J, Geary D, deVeber G. Cerebral sinovenous thrombosis and idiopathic nephrotic syndrome in childhood: report of four new cases and review of the literature. *Eur J Pediatr*. 2006;165(10):709-716. doi:10.1007/s00431-006-0147-7
76. Sellers A, Meoded A, Quintana J, et al. Risk factors for pediatric cerebral sinovenous thrombosis: a case-control study with case validation. *Thromb Res*. 2020;194:8-15. doi:10.1016/j.thromres.2020.06.013
77. Lane DA, Grant PJ. Role of hemostatic gene polymorphisms in venous and arterial thrombotic disease. *Blood*. 2000;95(5):1517-1532.
78. Khan S, Dickerman JD. Hereditary thrombophilia. *Thromb J*. 2006;4(15):234-236. doi:10.1186/1477-9560-4-15
79. Stone L, Ryba B, Wali A, Santiago-Dieppa D, Pannell JS. Superior anastomotic vein hypoplasia as a unique predisposing factor for cerebral venous hypertension and atraumatic non-aneurysmal subarachnoid hemorrhage: a case report, *Interdiscip Neurosurg*. 2021;25:101119. doi:10.1016/j.inat.2021.101119
80. Teksam M, Moharir M, deVeber G. Frequency and topographic distribution of brain lesions in pediatric cerebral venous thrombosis. *AJNR Am J Neuroradiol*. 2008;29(10):1961-1965. doi:10.3174/ajnr.A1246
81. Monagle P, Adams M, Mahonej M, et al. Outcome of pediatric thromboembolic disease: a report from the Canadian childhood thrombophilia registry. *Pediatr Res*. 2000;47(6):763-766. doi:10.1203/00006450-200006000-00013
82. Novak-Gottl U, Duering C, Kempf-Bielack B, Strater R. Thromboembolic diseases in neonates and children. *Pathophysiol Haemost Thromb* 2003;33(5-6):269-274. doi:10.1159/000083813
83. Wu YW, Hamrick SE, Miller SP. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. *Ann Neurol*. 2003;54(1):123-126. doi:10.1002/ana.10619
84. Marquardt G, Weidauer S, Lanfermann H. Cerebral venous sinus thrombosis manifesting as bilateral subdural effusion. *Acta Neurol Scand*. 2004;109(6):425-428.
85. Guerrero WR, Dandapat S, Ortega-Gutierrez S. Hemorrhagic cerebrovascular pathology in the pediatric population. *Front Neurol*. 2020;11:1055. doi:10.3389/fneur.2020.01055
86. Salih MA, Abdel-Galil M, Abdel-Gader AG, et al. Infectious and inflammatory disorders of the circulatory system as risk factors for stroke in Saudi children. *Saudi Med J*. 2006;27(1):41-52.
87. Hutchison JS, Ichord R, Guerguerian AM, DeVeber G. Cerebrovascular disorders. *Semin Pediatr Neurol*. 2004;11(2):139-146. doi:10.1016/j.spen.2004.04.004
88. Leonardi S, Pavone P, Rotolo N, La Rosa M. Stroke in two children with Mycoplasma pneumoniae infection. A causal or casual relationship? *Pediatr Infect Dis J*. 2005;24(9):843-845. doi:10.1097/01.inf.0000177284.88356.56
89. Kim GH, Seo WH, Je B-K, Eun S-H. Mycoplasma pneumoniae associated stroke in a 3-year-old girl. *Korean J Pediatr*. 2013;56(9):411-415. doi:10.3345/kjp.2013.56.9.411
90. Chang CJ, Chang WN, Huang LT, et al. Cerebral infarction in perinatal and childhood bacterial meningitis. *Q J Med*. 2003;96(10):755-762. doi:10.1093/qjmed/hcg128
91. Fraser S, Levy SM, Talebi Y, , et al. A national, electronic health record-based study of perinatal hemorrhagic and ischemic stroke. *J Child Neurol*. 2023;38(3-4):206-215. doi:10.1177/08830738231170739
92. Cognard C, Weill A, Lindgren S. Basilar artery occlusion in a child: «clot angioplasty» followed by thrombolysis. *Child's Nerv Sys*. 2000;16(8):496-500. doi:10.1007/s003819900197
93. Hranilovich JA, Park AH, Knackstedt ED, et al. Brain magnetic resonance imaging in congenital cytomegalovirus with failed newborn hearing screen. *Pediatr Neurol*. 2020;110:55-58. doi:10.1016/j.pediatrneurol.2020.05.006
94. Askarova AE, Zhurkabayeva BD. Hemorrhagic stroke in a child with cytomegaloviral infection. *Glob Pediatr Health*. 2022;9:1-5. doi:10.1177/2333794X211059412
95. Park YD, Belman AL, Kim TS, et al. Stroke in pediatric acquired immunodeficiency syndrome. *Ann Neurol*. 1990;28(3):303-311. doi:10.1002/ana.410280302
96. Benjamin LA, Bryer A, Emsley HCA, Khoo S, Solomon T, Connor MD. HIV infection and stroke: current perspectives and future directions. *Lancet Neurol*. 2012;11(10):878-890. doi:10.1016/S1474-4422(12)70205-3
97. Fullerton HJ, Elkind MS, Barkovich AJ, et al. The vascular effects of infection in pediatric stroke (VIPS) study. *J Child Neurol*. 2011;26(9):1101-1110. doi:10.1177/0883073811408089
98. Iannetti L, Zito R, Bruschi S, et al. Recent understanding on diagnosis and management of central nervous system vasculitis in children. *Clin Dev Immunol*. 2012;2012:698327. doi:10.1155/2012/698327
99. Fugate JE, Lyons JL, Thakur KT, Smith BR, Hedley-Whyte ET, Mateen FJ. Infectious causes of stroke. *Lancet Infect Dis*. 2014;14:869-880. doi:10.1016/S1473-3099(14)70755-8
100. Schoenberg BS, Mellinger JF, Schoenberg DG. Cerebrovascular disease in infants and children: a study of.incidence, clinical features, and survival. *Neurology*. 1978;28(8):763-768. doi:10.1212/wnl.28.8.763
101. Lopez-Yunez A, Garg B. Noninfectious cerebral vasculitis in children. *Semin Cerebrovasc Dis and Stroke*. 2001;1(3):249-263, doi:10.1053/scds.2001.27097
102. Benseler SM, deVeber G, Hawkins C, et al. Angiography-negative primary central nervous system vasculitis in children: a newly recognized inflammatory central nervous system disease. *Arthritis Rheum*. 2005;52(7):2159-2167. doi:10.1002/art.21144
103. Benseler SM, Silverman E, Aviv RI, Schneider R, Armstrong D. Primary central nervous system vasculitis in children. *Arthritis Rheum*. 2006;54(4):1291-1297. doi:10.1002/art.21766
104. Uziel Y, Laxer RM, Blaser S, Andrew M, Schneider R, Silverman ED. Cerebral vein thrombosis in childhood systemic lupus erythematosus. *J Pediatr*. 1995;126(5 Pt 1):722-727. doi:10.1016/s0022-3476(95)70399-3
105. Sokol DK, McIntyre JA, Short RA, et al. Henoch-Schonlein purpura and stroke: antiphosphatidylethanolamine antibody in CSF and serum. *Neurology*. 2000;55(9):1379-1381. doi:10.1212/wnl.55.9.1379
106. Honczarenko K, Ostanek L, Grzelec H, Fabian A, Fiedorowicz-Fabrycy I, Fryze C. Neurological deficits in patients with primary and secondary anticardiolipin syndrome. *Neurol Neurochir Pol*. 2001;35(3):395-404.
107. Morfín-Maciel B, Medina A, Rosales FE, Berrón R, Huerta Lopez J. Central nervous system involvement in a child with polyarteritis nodosa and severe atopic dermatitis. *Rev Alerg Mex*. 2002;49(6):189-195.
108. Fields CE, Bower TC, Cooper LT, et al. J. Takayasu's arteritis: operative results and influence of disease activity. *J Vasc Surg*. 2006;43(1):64-71. doi:10.1016/j.jvs.2005.10.010
109. Graf WD, Milstein JM, Sherry DD. Stroke and mixed connective tissue disease. *J Child Neurol*. 1993;8(3):256-259. doi:10.1177/088307389300800309
110. Fischer D, Haentjes J, Klein G, et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism: procedural and follow-up results after implantation of the Amplatzer®-occluder device. *J Intervent Cardiol*. 2011;24(1):85-91. doi:10.1111/j.1540-8183.2010.00593.x
111. Gaio G, Santoro G, Palladino MT, et al. Cardioembolic stroke: who is the guilty? *J Cardiovasc Med*. 2011;12(5):370-372. doi:10.2459/JCM.0b013e32833b9c4b
112. Mattle HP, Meier B, Nedeltchev K. Prevention of stroke in patients with patent foramen ovale. *Int J Stroke*. 2010;5(2):92-102. doi:10.1111/j.1747-4949.2010.00413.x
113. Menache CC, du Plessis AJ, Wessel DL, Jonas RA, Newburger JW. Current incidence of acute neurologic complications after open-heart operations in children. *Ann Thorac Surg*. 2002;73(6):1752-1758. doi:10.1016/s0003-4975(02)03534-8
114. Monagle P, Karl TR. Thromboembolic problems after the fontan operation. *Pediatr Card Surg Annu*. 2002;5:36-47. doi:10.1053/pcsu.2002.29716
115. Van den Bosch AE, Roos-Hesselink JW, van Domburg R, Bogers AC, Simoons ML, Meijboom FJ. Long-term outcome and quality of life in adult patients after the Fontan operation. *Am J Cardiol*. 2004;93(9):1141-1145. doi:10.1016/j.amjcard.2004.01.041
116. Procelewska M, Kolcz J, Januszewska K, Mroczek T, Malec E. Coagulation abnormalities and liver function after hemi-Fontan and Fontan procedures—the importance of hemodynamics in the early postoperative period. *Eur J Cardio Thorac Surg*. 2007;31(5):866-872. doi:10.1016/j.ejcts.2007.01.033
117. Domi T, Edgell DS, McCrindle BW, et al. Frequency, predictors, and neurologic outcomes of vaso-occlusive strokes associated with cardiac surgery in children. *Pediatrics*. 2008;122(6):1292-1298. doi:10.1542/peds.2007-1459
118. Lo W, Stephens J, Fernandez S. Pediatric stroke in the United States and the impact of risk factors. *J Child Neurol*. 2009;24(2):194-203. doi:10.1177/0883073808322665
119. Werho DK, Pasquali SK, Yu S, et al. Epidemiology of stroke in pediatric cardiac surgical patients supported with extracorporeal membrane oxygenation. *Ann Thorac Surg*. 2015;100(5):1751-1757. doi:10.1016/j.athoracsur.2015.06.020

120. Xi SB, Xie YM, Li T, Li YF, Qian MY, Zhang ZW. Pediatric hemorrhagic stroke complicates interventions for congenital heart disease: experiences from two centers. *Chin Med J (Engl)* 2018;131(23):2862-2863. doi:10.4103/0366-6999.246070
121. Kupferman JC, Lande MB, Stabouli S, Zafeiriou DI, Pavlakis SG. Hypertension and childhood stroke. *Pediatr Nephrol*. 2021;36(4):809-823. doi:10.1007/s00467-020-04550-2
122. Chiolero A, Cachat F, Burnier M, et al. Prevalence of hypertension in school-children based on repeated measurements and association with overweight. *J Hypertens*. 2007;25(11):2209-2217. doi:10.1097/HJH.0b013e3282ef48b2
123. Jordan LC, Kleinman JT, Hillis AE. Intracerebral hemorrhage volume predicts poor neurologic outcome in children. *Stroke*. 2009;40(5):1666-1671. doi:10.1161/STROKEAHA.108.541383
124. Lo JC, Sinaiko A, Chandra M, et al. Prehypertension and hypertension in community-based pediatric practice. *Pediatrics*. 2013;131(2):415-424. doi:10.1542/peds.2012-1292
125. Packer RJ, Rorke LB, Lange BJ, Siegel KR, Evans AE. Cerebrovascular accidents in children with cancer. *Pediatrics*. 1985;76(2):194-201.
126. Parasole R, Petruzziello F, Menna G, et al. Central nervous system complications during treatment of acute lymphoblastic leukemia in a single pediatric institution. *Leuk Lymphoma*. 2010;51(6):1063-1071. doi:10.3109/10428191003754608
127. Kuskonmaz B, Unal S, Gumruk F, Cetin M, Tuncer AM, Gurgey A. The neurologic complications in pediatric acute lymphoblastic leukemia patients excluding leukemic infiltration. *Leuk Res*. 2006;30(5):537-541. doi:10.1016/j.leukres.2005.09.009
128. Umeda K, Yoshida M, Suzuki N, et al. Complications in the central nervous system during chemotherapy for childhood acute lymphoblastic leukemia: JACLS ALL-02 study. *Rinsho Ketsueki*. 2007;48(3):204-211.
129. Noje C, Cohen K, Jordan LC. Hemorrhagic and ischemic stroke in children with cancer. *Pediatr Neurol*. 2013;49(4):237-242. doi:10.1016/j.pediatrneurol.2013.04.009
130. Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the childhood cancer survivor study. *J Clin Oncol*. 2006;24(33):5277-5282. doi:10.1200/JCO.2006.07.2884
131. Zadeh C, AlArab N, Muwakkit S, et al. Stroke in Middle Eastern children with cancer: prevalence and risk factors. *BMC Neurol*. 2022;22(1):31-35. doi:10.1186/s12883-022-02556-x
132. Kyrnetskiy EE, Kun LE, Boop FA, Sanford RA, Khan RB. Types, causes, and outcome of intracranial hemorrhage in children with cancer. *J Neurosurg*. 2005;102(1 Suppl):31-35. doi:10.3171/ped.2005.102.1.0031
133. DiMario FJ, Packer RJ. Acute mental status changes in children with systemic cancer. *Pediatrics*. 1990;85(3):353-360.
134. Campen CJ, Kranick SM, Kasner SE, et al. Cranial irradiation increases risk of stroke in pediatric brain tumor survivors. *Stroke*. 2012;43(11):3035-3040. doi:10.1161/STROKEAHA.112.661561
135. Haddy N, Mousannif A, Tukenova M, et al. Relationship between the brain radiation dose for the treatment of childhood cancer and the risk of long-term cerebrovascular mortality. *Brain*. 2011;134(Pt 5):1362-1372. doi:10.1093/brain/awr071
136. Nowak GU, Heinecke A, Kries R, Nurnberger W, Munchow N, Junker R. Thrombotic events revisited in children with acute lymphoblastic leukemia—impact of concomitant Escherichia coli asparaginase/prednisone administration. *Thromb Res*. 2001;103(3):165-172. doi:10.1016/s0049-3848(01)00286-9
137. Elhasid R, Lanir N, Sharon R, et al. Prophylactic therapy with enoxaparin during L-asparaginase treatment in children with acute lymphoblastic leukemia. *Blood Coagul Fibrinolysis*. 2001;12(5):367-370. doi:10.1097/00001721-200107000-00005
138. Reddy AT, Witek K. Neurologic complications of chemotherapy for children with cancer. *Curr Neurol Neurosci Rep*. 2003;3(2):137-142. doi:10.1007/s11910-003-0065-2
139. Kieslich M, Porto L, Lanfermann H, Jacobi G, Schwabe D, Bohles H. Cerebrovascular complications of L-asparaginase in the therapy of acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2003;25(6):484-487. doi:10.1097/00043426-200306000-00011
140. Uszynski M, Osinska M, Zekanowska E, Ziolkowska E. Children with acute lymphoblastic leukemia: is there any subgroup of children without elevated thrombin generation? A preliminary study utilizing measurements of thrombi-nantithrombin III complexes. *Med Sci Mon Int Med J Exp Clin Res*. 2000;6(1):108-111.
141. Omura M, Aida N, Sekido K, Kakehi M, Matsubara S. Large intracranial vessel occlusive vasculopathy after radiation therapy in children: clinical features and usefulness of magnetic resonance imaging. *Int J Radiat Oncol Biol Phys*. 1997;38(2):241-249. doi:10.1016/s0360-3016(97)82497-2
142. Fouladi M, Langston J, Mulhern R, et al. Silent lacunar lesions detected by magnetic resonance imaging of children with brain tumors: a late sequela of therapy. *J Clin Oncol*. 2000;18(4):824-831. doi:10.1200/JCO.2000.18.4.824
143. Penagaricano JA, Linskey ME, Ratanatharathorn V. Accelerated cerebral vasculopathy after radiation therapy to the brain. *Neurol India*. 2004;52(4):482-486.
144. Powars D, Wilson B, Imbus C, Pegelow C, Allen J. The natural history of stroke in sickle cell disease. *Am J Med*. 1978;65(3):461-471. doi:10.1016/0002-h9343(78)90772-6
145. Strouse JJ, Hulbert ML, DeBaun MR, et al. Primary hemorrhagic stroke in children with sickle cell disease is associated with recent transfusion and use of corticosteroids. *Pediatrics*. 2006;118(5):1916-1924. doi:10.1542/peds.2006-1241
146. Cancio MI, Helton KJ, Schreiber JE, Smeltzer MP, Kang G, Wang WC. Silent cerebral infarcts in very young children with sickle cell anaemia are associated with a higher risk of stroke. *Br J Haematol*. 2015;171(1):120-129. doi:10.1111/bjh.13525
147. Marks LJ, Munube D, Kasirye P, et al. Stroke prevalence in children with sickle cell disease in sub-saharan Africa: a systematic review and meta-analysis. *Glob Pediatr Health*. 2018;5. doi:10.1177/2333794X18774970
148. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*. 1998;91(1):288-294. doi:10.1182/blood
149. Rothman SM, Fulling KH, Nelson JS. Sickle cell anemia and central nervous system infarction: a neuropathological study. *Ann Neurol*. 1986;20(6):684-690. doi:10.1002/ana.410200606
150. Adams RJ, McKie VJ, Hsu L. Prevention of first stroke by transfusion in children with sickle cell anemia and abnormal results on transcranial Doppler. *N Engl J Med*. 1998;339(1):5-11. doi:10.1056/NEJM199807023390102
151. Preul MC, Cendes F, Just N, Mohr G. Intracranial aneurysms and sickle cell anemia: ultiplicity and propensity for the vertebrobasilar territory. *Neurosurgery*. 1998;42(5):971-997. doi:10.1097/00006123-199805000-00007
152. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med*. 2017;376(16):1561-1573. doi:10.1056/NEJMra1510865
153. Yilmaz EY, Pritz MB, Bruno A, Lopez-Yunez A, Moyamoya BJ. Indiana niversity medical center experience. *Arch Neurol*. 2001;58(8):1274-1278. doi:10.1001/archneur.58.8.1274
154. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. *N Engl J Med*. 2009;360(12):1226-1237. doi:10.1056/NEJMra0804622
155. Emerick KM, Krantz ID, Kamath BM, et al. Intracranial vascular abnormalities in patients with alagille syndrome. *J Pediatr Gastroenterol Nutr*. 2005;41(1):99-107. doi:10.1097/01.mpg.0000162776.67758.2f
156. Olds MV, Griebel RW, Hoffman HJ. The surgical treatment of childhood moyamoya disease. *J Neurosurg*. 1987;66(5):675-680. doi:10.3171/jns.1987.66.5.0675
157. Freundlich CL, Cervantes-Arslanian AM, Dorfman DH. Pediatric stroke emerg. *Med Clin N Am* 2012;30(3):805-828. doi:10.1016/j.emc.2012.05.005
158. Levin S. Moyamoya disease. *Dev Med Child Neurol*. 2008;24(6):850-853. doi:10.1111/j.1469-8749.1982.tb13707.x
159. Nagiub M, Allarakhia I. Pediatric moyamoya disease. *Am J Case Rep* 2013;3(14):134-138. doi:10.12659/AJCR.889170
160. Saarela M, Mustanoja S, Pekkola J, et al. Moyamoya vasculopathy - patient demographics and characteristics in the finnish population. *Int J Stroke*. 2017;12(1):90-95. doi:10.1177/1747493016669847
161. Frič R, Sorteberg A, Wallace S, Alonso AS, Due-Tønnessen BJ, Wiedmann M. Moyamoya disease in children. *Tidsskr Nor Laegeforen*. 2022;26(13):142. doi:10.4045/tidsskr.21.0776
162. Hillier CE, Collins PW, Bowen DJ, Bowley S, Wiles CM Inherited prothrombotic risk factors and cerebral venous thrombosis. *QJM*. 1998;91(10):677-680. doi:10.1093/qjmed/91.10.677
163. Vorstman E, Keeling D, Leonard J, Pike M. Sagittal sinus thrombosis in a teenager: homocystinuria associated with reversible antithrombin deficiency. *Dev Med Child Neurol*. 2002;44(7):498. doi:10.1017/s0012162201222427
164. Undas A, Williams EB, Butenas S, Orfeo T, Mann KG. Homocysteine inhibits inactivation of factor Va by activated protein C. *J Biol Chem*. 2001;276(6):4389-4397. doi:10.1074/jbc.M004124200
165. Kelly PJ, Furie KL, Kistler JP, et al. Stroke in young patients with hyperhomocysteinemia due to cystathionine beta-synthase deficiency. *Neurology*. 2003;60(2):275-279. doi:10.1212/01.WNL.0000042479.55406.B3
166. Mivakis S, Locshin MD, Atsumi T, et al. International consensus Statement on an update of the classification criteria for definite antiphospolipid syndrome. *J Thromb Haemost* 2006;4(2):295-306. doi:10.1111/j.1538-7836.2006.01753
167. Sazci A, Ergul E, Tuncer N, Akpinar G, Kara I. Methylenetetrahydrofolate reductase gene polymorphisms are associated with ischemic and hemorrhagic stroke: ual effect of MTHFR polymorphisms C677T and A1298C. *Brain Res Bull*. 2006;71(1-3):45-50. doi:10.1016/j.brainresbull.2006.07.014
168. Zou XL, Yao TX, Deng L, Chen L, Li Y, Zhang L. A systematic review and meta-analysis expounding the relationship between methylene tetrahydrofolate reductase gene polymorphism and the risk of intracerebral hemorrhage among populations. *Front Genet*. 2022;3:13-18. doi:10.3389/fgene.2022.829672
169. Ravelli A, Martini A Antiphospholipid syndrome in pediatrics. *Rheum Dis Clin North Am* 2007;33(3):499-523. doi:10.1016/j.rdc.2007.07.001
170. Hanly JG. Antiphospholipid syndrome. *CMAJ (Can Med Assoc J)*. 2003;168(13):1675-1682.

171. Heshmat NM, El-Kerdany TH. Serum levels of vascular endothelial growth factor in children and adolescents with systemic lupus erythematosus. *Pediatr Allergy Immunol*. 2007;18(4):346-353. doi:10.1111/j.1399-3038.2006.00510.x
172. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. *N Engl J Med*. 1998;338(25):1793-1797. doi:10.1056/NEJM199806183382502
173. Avcin T, Cimaz R, Silverman ED, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. *Pediatrics*. 2008;122(5):1100-1107. doi:10.1542/peds.2008-1209
174. Piette JC, Cervera R, Font J. Antiphospholipid syndrome: clinical and immunologic manifistations and patterns of disease expression in a cohort of 1000 patients. *Arthritis Rheum*. 2002;46(4):1019-1027. doi:10.1002/art.10187
175. Lynch DS, Wade C, De Paiva ARB, et al. Practical approach to the diagnosis of adult-onset leukodystrophies: an updated guide in the genomic era. *J Neurol Neurosurg Psychiatry*. 2018;90(5):543-554. doi:10.1136/jnnp-2018-319481
176. Elbaz A, Cambien F, Amareco P. On Behalpf of the Genic Investigahrs. Plasmoden activator inhibitor genotype and brain infarction. *Circulation*. 2001;103(2):13-15. doi:10.1161/01.cir.103.2.e13
177. Tabarki B, Hakami W, Alkhuraish N, Graies-Tlili K, Nashabat M, Alfadhel M. Inherited metabolic causes of stroke in children: mechanisms, types, and management. *Front Neurol*. 2021;12:633119. doi:10.3389/fneur.2021.633119
178. Testai FD, Gorelick PB. Inherited metabolic disorders and stroke part 1: Fabry disease and mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes. *Arch Neurol*. 2010;67(1):19-24. doi:10.1001/archneurol.2009.309
179. Testai FD, Gorelick PB. Inherited metabolic disorders and stroke part 2: homocystinuria, organic acidurias, and urea cycle disorders. *Arch Neurol*. 2010;67(2):148-153. doi:10.1001/archneurol.2009.333
180. Bachta R, Nyban W. Carnitine in adolescents. *J Adolese Health* 1993;14(6):440-441. doi:10.1016/1054-139X(93)90114-5
181. Shirokostyuk LA. Acute disorders of cerebral circulation in childhood at the stage of emergency medical care. *Health and Disease*. 2011;98:85-87. (In Russian).
182. Sandberg DI, Lamberti-Pasculli M, Drake JM, Humphreys RP, Rutka JT. Spontaneous intraparenchymal hemorrhage in full-term neonates. *Neurosurgery*. 2001;48(5):1042-1048. doi:10.1097/00006123-200105000-00015
183. Elbers J, Viero S, MacGregor D, DeVeber G, Moore AM. Placental pathology in neonatal stroke. *Pediatrics*. 2011;127(3):722-729. doi:10.1542/peds.2010-1490
184. Harbert MJ, Jett M, Appelbaum M, Nass R, Trauner DA. Perinatal risk factors and later social, thought, and attention problems after perinatal stroke. *Stroke Res Treat*. 2012;2012:914546. doi:10.1155/2012/914546
185. Porcari GS, Jordan LC, Ichord RN, Licht DJ, Smith SE, Beslow LA. Outcome rajectories after primary perinatal hemorrhagic stroke. *Pediatr Neurol*. 2020;105:41-47. doi:10.1016/j.pediatrneurol.2019.11.019
186. Xia Q, Yang Z, Xie Y, et al. The incidence and characteristics of perinatal stroke in Beijing: A multicenter study. *Front Public Health*. 2022;10:783153. doi:10.3389/fpubh.2022.783153
187. Roy B, Webb A, Walker K, Morgan C, Badawi N, Novak I. Risk factors for perinatal stroke in term infants: a case-control study in Australia. *J Paediatr Child Health*. 2023;59(4):673-679. doi:10.1111/jpc.16372
188. Cooles P, Michaud R. Stroke after heavy cannabis smoking. *Postgrad Med*. 1987;63(740):511-516. doi:10.1136/pgmj.63.740.511
189. White D, Martin D, Geller T, Pittman T. Stroke associated with marijuana abuse. *Pediatr Neurosurg*. 2000;32(2):92-94. doi:10.1159/000028906
190. Ibraim da Freiria Elias KM, Leme de Moura-Ribeiro MV. Stroke caused auditory attention deficits in children. Acidente vascular cerebral causa défices da atenção seletiva auditiva em crianças. *Arq Neuro-Psiquiatr* 2013;71(1):11-17. doi:10.1590/S0004-282X2012005000018
191. Fox CK, Johnston C, Sidney S, Fullerton HJ. High critical care usage due to pediatric stroke. *Neurology*. 2012;79(5):420427. doi:10.1212/WNL.0b013e3182616fd7
192. Beslow LA, Abend NS, Gindville MC, et al. Pediatric intracerebral hemorrhage: acute symptomatic seizures and epilepsy. *JAMA Neurol*. 2013;70(4):448-454. doi:10.1001/jamaneurol.2013.1033
193. Jordan LC, Hillis AE. Hemorrhagic stroke in children. *Pediatr Neurol*. 2007;36(2):73-80. doi:10.1016/j.pediatrneurol.2006.09.017
194. Calder K, Kokorowski P, Tran T, Henderson S. Emergency department presentation of pediatric stroke. *Pediatr Emerg Care*. 2003;19(5):320-328. doi:10.1097/01.pec.0000092577.40174.61
195. Schwarz S, Hafner K, Aschoff A, Schwab S. Incidence and prognostic significance of fever following intracerebral hemorrhage. *Neurology*. 2000;54(2):354-361. doi:10.1212/wnl.54.2.354
196. Lviv OA, Kovtun OP, Lushina MN, Sulimov AV. Kliniko-epidemiologichesky features of a course of strokes at children. *Neurosurgery and Neurology of Children's Age*. 2013;2(7).
197. Tsze1 DS, Jonathan HV. Pediatric stroke: a review. *Emerg Med Int*. 2011;10:734506. doi:10.1155/2011/734506
198. Hey G, Guyot M, Carter A, Lucke-Wold B. Augmented reality in neurosurgery: a new paradigm for training. *Medicina (Kaunas)*. 2023:59(10): 1721. doi:10.3390/medicina59101721
199. Monagle P, Chan KC, Deveber G, Malmberg K, Decker BC. *Pediatric Thromboembolism and Stroke*. 1st ed Hamilton, ON: B.C. Decker, 2006.
200. Treib J, Grauer MT, Woessner R, Morgenthaler M. Treatment of stroke on an intensive stroke unit: a novel concept. *Intensive Care Med*. 2000;26(11):1598-1611. doi:10.1007/s001340000667
201. Adams H, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American heart association/American stroke association stroke ouncil, clinical ardiology ouncil, cardiovascular adiology and intervention ouncil, and the atherosclerotic peripheral vascular disease and quality of care outcomes in research nterdisciplinary working groups: the American cademy of eurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38(5):1655-1711. doi:10.1161/STROKEAHA.107.181486
202. Wang X, Sandset EC, Moullaali TJ, et al. Determinants of the high admission blood pressure in mild-to-moderate acute intracerebral hemorrhage. *J Hypertens*. 2019;37(7):1463-1466. doi:10.1097/HJH.0000000000002056
203. Qureshi AI, Palesch YY, Martin R, et al. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the antihypertensive treatment of acute cerebral hemorrhage study. *Arch Neurol*. 2010;67(5):570-576. doi:10.1001/archneurol.2010.61
204. The blood pressure in acute stroke collaboration (BASC). Vasoactive drugs for acute stroke (Cochrane review). The Cochrane Library. 2002;4.
205. Weir CJ, Murray GD, Dyker AG, Lees KR Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. *BMJ (Clinical research ed)*. 1997;314(7090):1303-1306. doi:10.1136/bmj.314.7090.1303
206. Fujimura M, Tominaga T. Diagnosis of moyamoya disease: international tandard and egional ifferences. *Neurol Med -Chir*. 2015;55(3):189-193. doi:10.2176/nmc.ra.2014-0307
207. Rivkin MJ, Bernard TJ, Dowling MM, Lefond CA. Guidelines for urgent management of stroke in children. *Pediatr Neurol*. 2016;56(8):17-22. doi:10.1016/j.pediatrneurol.2016.01.016
208. Bederson JB, Connolly ESJ, Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 2009;40(3):994-1025. doi:10.1161/STROKEAHA.108.191395
209. Rinkel GJE, Feigin VL, Algra A, Vermeulen M, van Gijn J. Calcium antagonists for aneurysmal subarachnoid haemorrhage (Cochrane Review). The Cochrane Library, 4; 2002.
210. Thyagarajan B, Tillqvist E, Baral V. Minimal enteral nutrition during neonatal hypothermia treatment for perinatal hypoxic-ischaemic encephalopathy is safe and feasible. *Act Paediatr*. 2015;104(2):146-151. doi:10.1111/apa.12838
211. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. *Stroke*. 2002;33(1):136-140. doi:10.1161/hs0102.100877
212. Gonda DD, Meltzer HS, Crawford JR, et al. Complications associated with prolonged hypertonic saline therapy in children with elevated intracranial pressure. *Pediatr Crit Care Med*. 2013;14(6):610-620. doi:10.1097/PCC.0b013e318291772b
213. Venkatasubramanian C, Mlynash M, Finley-Caulfield A, et al. Natural history of perihematomal edema after intracerebral hemorrhage measured by serial magnetic resonance imaging. *Stroke*. 2011;42(1):73-80. doi:10.1161/STROKEAHA.110.590646
214. Jordan LC, Hillis AE. Challenges in the diagnosis and treatment of pediatric stroke. *Nat Rev Neurol*. 2011;7(4):199-208. doi:10.1038/nrneurol.2011.23
215. Gebel JM, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S. Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke*. 2002;33(11):2631-2635. doi:10.1161/01.str.0000035284.12699.84
216. Diringer MN, Zazulia AR. Osmotic therapy: fact and fiction. *Neurocrit Care* 2004;1(2):219-233. doi:10.1385/NCC:1:2:219
217. Rapoport SI. Osmotic opening of the blood-brain barrier: principles, mechanism, and therapeutic applications. *Cell Mol Neurobiol*. 2000;20(2):217-230. doi:10.1023/a:1007049806660
218. Joshi S, Singh-Moon R, Wang M, Bruce JN, Bigio IJ, Mayevsky A. Real-time hemodynamic response and mitochondrial function changes with intracarotid mannitol injection. *Brain Res*. 2014;26(1549):42-51. doi:10.1016/j.brainres.2013.12.036
219. Qureshi AI, Wilson DA, Traystman RJ. Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: comparison between mannitol and hypertonic saline. *Neurosurgery*. 1999;44(5):1055-1063. doi:10.1097/00006123-199905000-00064
220. Thenuwara K, Todd MM, Brian JEJ. Effect of mannitol and furosemide on plasma osmolality and brain water. *Anesthesiology*. 2002;96(2):416-421. doi:10.1097/00000542-200202000-00029
221. Mayzler O, Leon A, Eilig I, et al. The effect of hypertonic (3%) saline with and without furosemide on plasma osmolality, sodium concentration, and brain water

content after closed head trauma in rats. *J Neurosurg Anesthesiol*. 2006;18(1):24-31. doi:10.1097/01.ana.0000188358.41284.cb
222. Tuor UI, Simone CS, Barks JD, Post M. Dexamethasone prevents cerebral infarction without affecting cerebral blood flow in neonatal rats. *Stroke*. 1993;24(3):452-457. doi:10.1161/01.str.24.3.452
223. Greenberg MS. *Handbook of Neurosurgery*. 3rd ed. 2020:1013.
224. Cheng WC, Chung CY, Lee MH, et al. Dexamethasone reduces brain cell apoptosis and inhibits inflammatory response in rats with intracerebral hemorrhage. *J Neurosci Res*. 2015;93(1):178-188. doi:10.1002/jnr.23454
225. Poungvarin N, Bhoopat W, Viriyavejakul A, et al. Effects of dexamethasone in primary supratentorial intracerebral hemorrhage. *N Engl J Med*. 1987;316(20):1229-1233. doi:10.1056/NEJM198705143162001
226. Passero S, Ciacci G, Ulivelli M. The influence of diabetes and hyperglycemia on clinical course after intracerebral hemorrhage. *Neurology*. 2003;61(10):1351-1356. doi:10.1212/01.wnl.0000094326.30791.2d
227. Myles LM, Massicotte P, Drake J. Intracranial hemorrhage in neonates with unrecognized hemophilia A: a persisting problem. *Pediatr Neurosurg*. 2001;34(2):94-97. doi:10.1159/000056001
228. Olivieri C, Crocoli A, De Pasquale MD, Inserra A. Central venous catheter placement in children with thrombocytopenia. *Minerva Pediatr*. 2016;68(6):398-403.
229. Elgendy AI, Ismail AM, Elhawary E, et al. Insertion of central venous catheters in children undergoing bone marrow transplantation: is there a platelet level for a safe procedure? *Ann Pediatr Surg*. 2020;16:46.
230. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352(8):777-785. doi:10.1056/NEJMoa042991
231. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA*. 2006;295(3):293-298. doi:10.1001/jama.295.3.293
232. Gabis LV, Yangala R, Lenn NJ. Time lag to diagnosis of stroke in children. *Pediatrics*. 2002;110(5):924-928. doi:10.1542/peds.110.5.924
233. Naff NJ, Hanley DF, Keyl PM, et al. Intraventricular thrombolysis speeds blood clot resolution: results of a pilot, prospective, randomized, double-blind, controlled trial. *Neurosurgery*. 2004;54(3):577-584. doi:10.1227/01.NEU.0000108422.10842.60
234. Rawanduzy CA, Earl E, Mayer G, Lucke-Wold B. *Biomedicines*. 2023;11(1):2. doi:10.3390/biomedicines11010002
235. Pisani F, Fusco C, Nagarajan L, Spagnoli C. Acute symptomatic neonatal seizures, brain injury, and long-term outcome: the role of neuroprotective strategies. *Expert Rev Neurother*. 2021;21(2):189-203. doi:10.1080/14737175.2021.1848547
236. Abend NS, Topjian AA, Gutierrez-Colina AM, Donnelly M, Clancy RR, Dlugos DJ Impact of continuous EEG monitoring on clinical management in critically ill children. *Neurocrit Care*. 2011;15(1):70-75. doi:10.1007/s12028-010-9380-z
237. Bassan H, Bental Y, Shany E, et al. Neonatal seizures: dilemmas in workup and management. *Pediatr Neurol*. 2008;38(6):415-421. doi:10.1016/j.pediatrneurol.2008.03.003
238. Janet SS, Bergin AM, Stopp C, et al. A pilot randomized, controlled, double-blind trial of umetanide to treat neonatal seizures. *Ann Neurol*. 2021;89(2):327-340. doi:10.1002/ana.25959
239. Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med*. 1999;341(7):485-489. doi:10.1056/NEJM199908123410704
240. Boylan GB, Rennie JM, Chorley G, et al. Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. *Neurology*. 2004;62(3):486-488. doi:10.1212/01.wnl.0000106944.59990.e6
241. Govaert P, Dudink J, Visser G, Breukhoven P, Vanhatalo S, Lequin M. Top of the basilar artery embolic stroke and neonatal myoclonus. *Dev Med Child Neurol*. 2009;51(4):324-327. doi:10.1111/j.1469-8749.2008.03183.x
242. Weeke LC, Toet MC, van Rooij LGM, et al. Lidocaine response rate in aEEG-confirmed neonatal seizures: retrospective study of 413 full-term and preterm infants. *Epilepsia*. 2016;57(2):233-242. doi:10.1111/epi.13286
243. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol*. 2007;22(1):95-98. doi:10.1177/0883073807299973
244. Manthey D, Asimiadou S, Stefovska V, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. *Exp Neurol*. 2005;193(2):497-503. doi:10.1016/j.expneurol.2005.01.006
245. Mbizvo GK, Dixon P, Hutton JL, Marson AG. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. *Cochrane Database Syst Rev*. 2012;9:CD001901. doi:10.1002/14651858.CD001901.pub2
246. Talos DM, Chang M, Kosaras B, et al. Antiepileptic effects of levetiracetam in a rodent neonatal seizure model. *Pediatr Res*. 2013;73(1):24-30. doi:10.1038/pr.2012.151
247. Armstrong-Wells J, Ferriero DM. Diagnosis and acute management of perinatal arterial ischemic stroke. *Neurol Clin Pract*. 2014;4(5):378-385. doi:10.1212/CPJ.0000000000000077
248. Sortino V, Marino S, Praticò A, et al. Efficacy of the anti-seizure medications in acute symptomatic neonatal seizures caused by stroke. A systematic review. *Acta Biomed*. 2022;93(6):e2022328. doi:10.23750/abm.v93i6.13440
249. Minnerup J, Sutherland BA, Buchan AM, Kleinschnitz C. Neuroprotection for stroke: current status and future perspectives. *Int J Mol Sci*. 2012;13(9):11753-11772. doi:10.3390/ijms130911753
250. Gross BA, Storey A, Orbach DB, Scott RM, Smith ER. Microsurgical treatment of arteriovenous malformations in pediatric patients: the Boston Children's Hospital experience. *J Neurosurg Pediatr*. 2015;15(1):71-77. doi:10.3171/2014.9.PEDS146
251. Adams RJ, Brambilla D. Optimizing primary stroke prevention in sickle cell anemia trial I., iscontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. *N Engl J Med*. 2005;353(26):2769-2778. doi:10.1056/NEJMoa050460
252. Enninful-Eghan H, Moore RH, Ichord R, Smith-Whitley K, Kwiatkowski JL. Transcranial Doppler ultrasonography and prophylactic transfusion program is effective in preventing overt stroke in children with sickle cell disease. *J Pediatr*. 2010;157(3):479-484. doi:10.1016/j.jpeds.2010.03.007
253. Lee MT, Piomelli S, Granger S, et al. Stroke prevention trial in sickle cell anemia (STOP): extended follow-up and final results. *Blood*. 2006;108(3):847-852. doi:10.1182/blood-2005-10-009506
254. Kassim AA, Galadanci NA, Pruthi S, DeBaun MR. How I treat and manage strokes in sickle cell disease. *Blood*. 2015;125(22):3401-3410. doi:10.1182/blood-2014-09-551564
255. Kanter J, Walters MC, Krishnamurti L, et al. Biologic and clinical efficacy of LentiGlobin for sickle cell disease. *N Engl J Med*. 2021;386(7):617-628. doi:10.1056/NEJMoa2117175
256. Lynch JK, Han CJ. Pediatric stroke: what do we know and what do we need to know? *Semin Neurol*. 2005;25(4):410-423. doi:10.1055/s-2005-923535
257. DeVeber G. In pursuit of evidence-based treatments for paediatric stroke: the UK and Chest guidelines. *Lancet Neurol*. 2005(4:7):432-436. doi:10.1016/S1474-4422(05)70120-4
258. Blom I, De Schryver EL, Kappelle LJ, et al. Prognosis of haemorrhagic stroke in childhood: a long-term follow-up study. *Dev Med Child Neurol*. 2003;45(4):233-239. doi:10.1017/s001216220300046x
259. Nelson MD Jr, Maeder MA, Usner D, et al. Prevalence and incidence of intracranial haemorrhage in a population of children with haemophilia. *The Hemophilia Growth and Development Study Haemophilia*. 1999; 5(5):306-312. doi:10.1046/j.1365-2516.1999.00338.x
260. Neuner B, von Mackensen S, Krümpel A. Health-related quality of life in children and adolescents with stroke, self-reports, and parent/proxies reports: cross-sectional investigation. *Ann Neurol*. 2011;70(1):70-78. doi:10.1002/ana.22381
261. Trauner DA, Chase C, Walker P, Wulfeck B. Neurologic profiles of infants and children after perinatal stroke. *Pediatr Neurol*. 1993;9(5):383-386. doi:10.1016/0887-8994(93)90107-n
262. Bruno CJ, Beslow LA, Witmer CM, et al. Haemorrhagic stroke in term and late preterm neonates. *Arch Dis Child Fetal Neonatal Ed*. 2014;99(1):383. doi:10.1136/archdischild-2013-304068
263. Beslow L, Storm PB, Licht DJ, Smith S. Hemorrhage volume is a predictor of short-term outcome in pediatric spontaneous intracerebral hemorrhage: a prospective consecutive cohort study. *Stroke*. 2009;40:e125.
264. Fullerton HJ, Chetkovich DM, Wu YW, Smith WS, Johnston SC. Deaths from stroke in US children, 1979 to 1998. *Neurology*. 2002;59(1):34-39. doi:10.1212/wnl.59.1.34
265. Lo WD, Hajek C, Pappa C, Wang W, Zumberge N. Outcomes in children with hemorrhagic stroke. *JAMA Neurol*. 2013;70(1):66-71. doi:10.1001/jamaneurol.2013.577
266. Statler KD, Dong L, Nielsen DM, Bratton SL. Pediatric stroke: clinical characteristics, acute care utilization patterns, and mortality. *Childs Nerv Syst*. 2011;27(4):565-573. doi:10.1007/s00381-010-1292-x
267. Adil MM, Qureshi AI, Beslow LA, Malik AA, Jordan LC. Factors associated with increased in-hospital mortality among children with intracerebral hemorrhage. *J Child Neurol*. 2015;30(8):1024-1028. doi:10.1177/0883073814552191
268. Kleindorfer D, Khoury J, Kissela B, et al. Temporal trends in the incidence and case fatality of stroke in children and adolescents. *J Child Neurol*. 2006;21(5):415-418. doi:10.1177/08830738060210050301
269. Lovelock CE, Rinkel GJ, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: population-based study and systematic review. *Neurology*. 2010;74(19):1494-1501. doi:10.1212/WNL.0b013e3181dd42b3