Journal of Neurology (2019) 266:2929–2941
https://doi.org/10.1007/s00415-019-09508-5

ORIGINAL COMMUNICATION

Arterial ischemic stroke in infants, children, and adolescents: results of a Germany-wide surveillance study 2015–2017

Lucia Gerstl[1] · Raphael Weinberger[2] · Florian Heinen[1] · Michaela V. Bonfert[1] · Ingo Borggraefe[1] · A. Sebastian Schroeder[1] · Moritz Tacke[1] · Mirjam N. Landgraf[1] · Katharina Vill[1] · Karin Kurnik[3] · Anna-Lisa Sorg[2] · Martin Olivieri[3]

Received: 18 March 2019 / Revised: 1 August 2019 / Accepted: 13 August 2019 / Published online: 23 August 2019

Abstract

Objective Childhood arterial ischaemic stroke (AIS) is rare, but causes significant morbidity and mortality. We aimed to investigate incidence, age-dependent clinical presentation, and risk factors and to discuss the medical care situation in Germany.

Methods This prospective epidemiological study was conducted via ESPED (Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland), a hospital-based German nation-wide surveillance unit for rare pediatric diseases. Children aged 28 days–18 years with first AIS between January 2015 and December 2017 were included.

Results In the 3-year period, 164 children were reported. Incidence showed peaks in infants, children < 2 years of age, and adolescents (12–18 years), with a significant male predominance observed in adolescents only. Independent of age, most children (91%) presented with focal symptoms, particularly with acute hemiparesis. The occurrence of seizures in infants (57%) and more nonspecific symptoms in school-children and adolescents (54%) is considered noteworthy. Prothrombotic states (34%), cardiac disorders (29%), and arteriopathies (19%) were the most frequently identified risk factors. The majority of children (72/131, thus 55%) were discharged home after acute care phase. At time of discharge, most common neurological symptoms were hemiparesis (42%), facial palsy (15%), and speech disturbance (12%).

Conclusion This study provides population-based data of childhood AIS which may be useful for further research. The improvement of acute stroke management is needed for children, but also the standardization of post-stroke care in the outpatient setting has to be structured. Considering the higher stroke incidence in (male) adolescents, it is advisable to combine research activities in adolescents and young adults.

Keywords Childhood stroke · Pediatric stroke · Symptoms · Risk factors

Introduction

Childhood arterial ischemic stroke (AIS) differs in essential aspects from adult stroke. Pediatricians, among others, struggle with a low awareness among laypersons and physicians, resulting in delayed diagnosis, less experience in the use of thrombolysis and mechanical thrombectomy, and a time-and resource-consuming etiological clarification due to the multitude of possible risk factors [1–7].

The aim of this study was to provide data from Germany for the incidence, age-dependent clinical presentation, and risk factors for childhood AIS and to reflect the medical care situation for children with stroke regarding diagnostic work-up, hyperacute treatment, short-term outcomes, and follow-up.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09508-5) contains supplementary material, which is available to authorized users.

✉ Lucia Gerstl
lucia.gerstl@med.lmu.de

[1] Department of Pediatric Neurology and Developmental Medicine, LMU Munich, University Hospital, Dr. von Hauner Children`s Hospital, Lindwurmstr. 4, 80337 Munich, Germany

[2] Division of Epidemiology, Institute of Social Pediatrics and Adolescent Medicine, LMU Munich, Lindwurmstr. 4, 80337 Munich, Germany

[3] Department of Pediatric Hemostasis and Thrombosis, LMU Munich, University Hospital, Dr. von Hauner Children`s Hospital, Lindwurmstr. 4, 80337 Munich, Germany

Methods

Study population

From 1 January 2015 to 31 December 2017, the ESPED childhood stroke study group enrolled infants, children, and adolescents (aged 28 days–18 years) with first AIS in Germany. The diagnosis was given by the treating pediatrician. Exclusion criteria were (presumed) perinatal/neonatal stroke, hemorrhagic stroke, cerebral sinovenous thrombosis, and presumed transient ischemic attack.

Reporting system

Patients eligible for inclusion were identified via ESPED (acronym for: Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland), a hospital-based nation-wide surveillance system for rare pediatric diseases founded in 1992. Every month, all participating children's hospitals and pediatric departments ($n=345$) were asked via e-mail or postcard to report the number of children admitted with first AIS (including a null option). Pediatricians reporting new cases were requested to fill out a study-specific, anonymous questionnaire, based on the child´s medical record. As there was no standardized investigation protocol, diagnostic work-up as well as treatment were at the discretion of the treating pediatricians.

All questionnaires were checked for plausibility by a pediatric neurologist (LG) and specialist for pediatric hemostaseology (MO).

The case report form included information about demographic variables, presenting features, risk factors, diagnostics, imaging results, treatment, short-term outcomes and follow-up care, among other variables. The questionnaire developed for this study can be obtained in the English language version as a supplementary file.

Statistical analysis

For descriptive statistics, we used SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). Proportions were compared using Chi-square statistics. p values <0.05 were considered significant. For estimating incidence, population data from the Federal Statistical Office for children under 18 years (2015–2017) were used [8]. We used the method described by Armitage and Berry to calculate the 95% confidence interval (95% CI) for incidence estimates.

Ethical approval

The study was approved by the ethics committee and data protection commissioner of the Medical Faculty of the Ludwig-Maximilians-University Munich, Number 42-15 (05-04-2015).

Results

Population characteristics

In the 3-year study period, 164 cases of first AIS were reported, with completed questionnaires, accounting for an overall incidence of 0.41/100,000 per year (95% CI 0.347; 0.474). Analysis of age showed a u-shaped distribution with peaks in infants, very young children, and adolescents. Estimate incidences were highest in children less than 1 year (0.60/100,000 per year; 95% CI 0.330; 1.013), compared with those aged 1–5 years (0.38/100,000 per year; 95% CI 0.274; 0.513), > 5–12 years (0.32/100,000 per year; 95% CI 0.226; 0.427), and > 12–18 years (0.48/100,000 per year; 95% CI 0.226; 0.427).

97 children were male (m:f = 1.44; $p=0.0191$). Higher incidence in males was highly significant in adolescents from 12 years onwards (m:f = 45:22; $p=0.005$), whereas sex-specific incidence was nearly equal in the younger age group (0 to < 12 years: m:f = 52:45; $p=0.4772$) (Fig. 1). Most of the children were Caucasian (86.6%), 5.5% were Asian, and 1.8% were African (missing data for 6,1% of cases).

Presenting symptoms

Table 1 shows the presenting symptoms for the whole sample and by age group.

Focal symptoms, in particular an acute hemiparesis, were the most common presenting features of childhood AIS, independent of age. Concomitant nonspecific symptoms such as headache, vertigo, vomiting, and decreased levels of consciousness were especially common in school-aged children and adolescents. More than half of infants presented with seizures.

Risk factors

One risk factor was reported in 59 (36%) children, two in 52 (32%) children, three in 12 (7%) children, and four in 1 (1%) child. Stroke was classified as cryptogenic (no known risk factor identified) in 40 (24%) children.

An overview of risk factor categories is given in Table 2. Prothrombotic states, cardiac diseases, and arteriopathies were most common. Especially, cardiac disorders are often described as a single risk factor (19/47 children), whereas coagulation problems often co-occur with other risk factors (43/56 children). Infectious diseases were seen in 19 children, of which 4 children did not show any additional risk factors. With exception of the risk factor categories arteriopathy ($p=0.0436$) and other ($p=0.0006$), categories did not differ significantly across different age

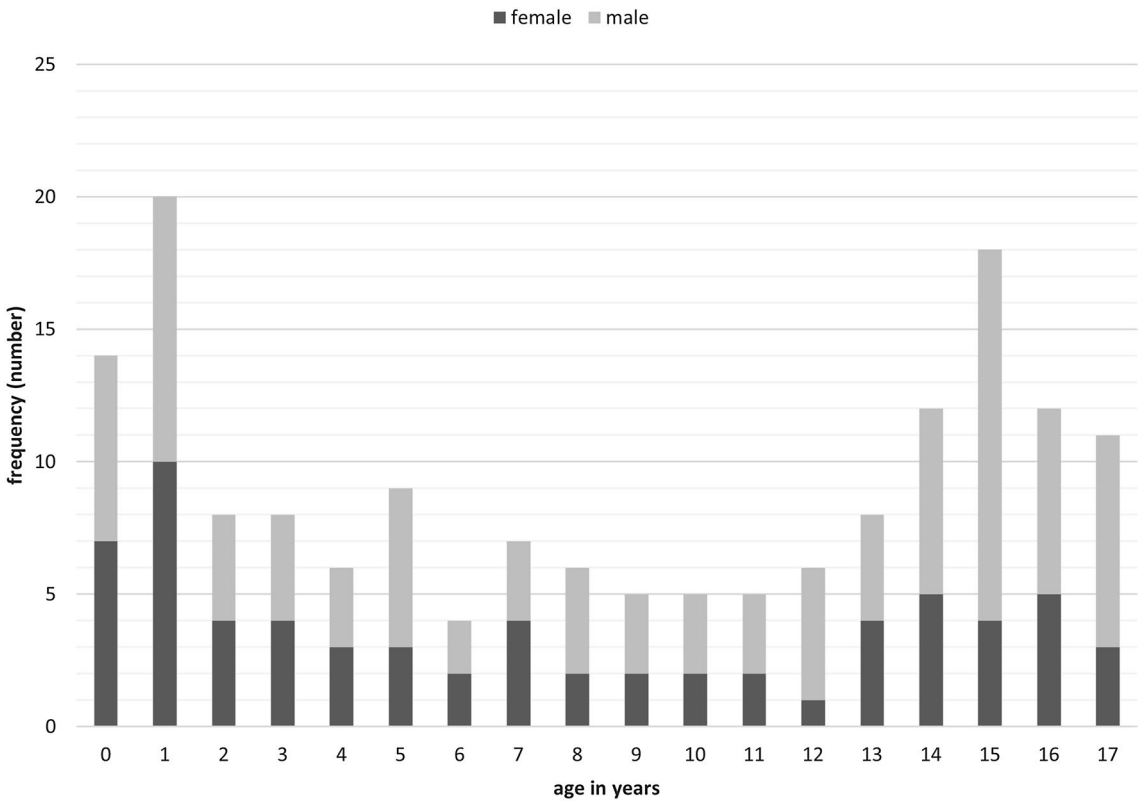

Fig. 1 Age and sex distribution of children with AIS ($n = 164$)

Table 1 Presenting symptoms in total and by age group ($n = 164$)

	Number of cases ($n = 164$)	< 1 year ($n = 14$)	1–5 years ($n = 42$)	6–18 years ($n = 108$)
Focal symptoms	**149 (91%)**	**10 (71%)**	**34 (81%)**	**105 (97%)**
Hemiparesis	110 (67%)	10 (71%)	28 (67%)	72 (67%)
Facial weakness	52 (32%)	4 (19%)	11 (26%)	37 (34%)
Speech disturbance	68 (41%)	–	10 (24%)	58 (54%)
Visual disturbance	32 (20%)	2(14%)	3 (7%)	27 (25%)
Ataxia	24 (15%)	–	6 (14%)	18 (17%)
Paresthesia	19 (12%)	1 (7%)	–	18 (17%)
Other focal symptoms	29 (18%)	2 (14%)	11 (26%)	16 (15%)
Nonspecific symptoms	**79 (48%)**	**2 (14%)**	**19 (45%)**	**58 (54%)**
Headache	39 (34%)	–	3 (7%)	36 (33%)
Decreased consciousness level	34 (21%)	–	13 (31%)	21 (19%)
Vomiting/ nausea	33 (20%)	2 (14%)	8 (19%)	23 (21%)
Vertigo	21 (13%)		2 (5%)	19 (18%)
Other nonspecific symptoms	5 (3%)	–	3 (7%)	2 (2%)
Seizure	**30 (18%)**	**8 (57%)**	**13 (31%)**	**9(8%)**

groups (Table 2). A detailed overview of described risk factors is shown in Table 3. This table separately shows which risk factors occurred in isolation.

Risk factors in adolescents

As male sex was highly significant in AIS incidence in adolescence (≥ 12 years), we compared risk factors reported for males vs females in this age group. We did not find a

Table 2 Prevalence of risk factor categories by age

Risk factor category	Number of cases ($n=164$)	0 to 12 months old ($n=14$)	1–5 years old ($n=42$)	5–12 years old ($n=41$)	12–18 years old ($n=67$)	p value
Cardiac	47 (29%)	6 (43%)	15 (36%)	8 (20%)	18 (27%)	0.2369
Prothrombotic state	56 (34%)	6 (43%)	13 (31%)	17 (42%)	20 (30%)	0.5238
Arteriopathy	31 (19%)	1 (7%)	7 (17%)	14 (34%)	9 (13%)	0.0436
Acute systemic	19 (12%)	3 (21%)	6 (14%)	6 (15%)	4 (6%)	0.1814
Hemato-oncological	15 (9%)	–	4 (10%)	3 (7%)	8 (12%)	0.6670
Metabolic	3 (2%)	–	1 (2%)	1 (2%)	1 (2%)	1.0000
Chronic head and neck disorders*	12 (7%)	–	2 (5%)	2 (5%)	8 (12%)	0.3867
Other**	13 (8%)	2 (14%)	9 (21%)	–	2 (3%)	0.0006
Cryptogenic***	40 (24%)	2 (14%)	8 (19%)	9 (22%)	21 (31%)	0.4078

*Brain tumor, aneurysms, arteriovenous malformations, migraine

**Connective tissue disorders, genetic disorders, previous brain surgery, trauma

***No risk factor reported

significant difference regarding the number of risk factors ($p=0.4025$) (Fig. 2). The only significant difference regarding risk factors was observed in the category "hemato-oncological diseases" [$p=0.0456$; reported diseases in 8 male adolescents: acute lymphatic leukemia ($n=3$), sickle cell disease ($n=1$), osteosarcoma ($n=1$), neuroblastoma ($n=1$), lymphoma ($n=1$), and pontine glioma ($n=1$)] (Fig. 3).

Neuroimaging

First imaging modalities were a CT in 25/146 children, CT plus CT angiography in 10/146 children, MRI in 48/146 children, MRI plus MR angiography in 58/164 children, and a transcranial ultrasound in 5/146 children (missing information or multiple applied imaging modalities $n=18$).

The lesion was right-sided in 58/137 children and left-sided in 65/137 children, and both sides were affected in 14/137 children (missing information $n=27$).

The middle cerebral artery was by far the most affected vessel (75/110 children), followed by the posterior cerebral artery (20/110 children) and the anterior cerebral artery (15/110 children). In 24/110 children, an abnormality was seen in more than one cerebral vessel (missing information $n=54$) (Table 4). Our data did not indicate a correlation between affected vessel and presenting clinical symptom.

Hyperacute therapy

29 children (18%) aged 0–16 years received hyperacute therapy (thrombolysis $n=11$, mechanical thrombectomy $n=10$, thrombolysis plus mechanical thrombectomy $n=8$). A bleeding complication was reported in one child. A detailed analysis of this for adults evidence-based treatment option is currently in preparation and will be published separately.

Secondary prevention

With respect to the secondary prevention, 16/145 children were discharged without any antithrombotic therapy (missing information in $n=19$). The majority of children (62/145 children) received low-weight heparine followed by ASS (45/145 children), ASS plus further anticoagulation (16/145 children), or Vitamin K antagonists (6/145 children).

Short-term outcomes and follow-up care

Most common neurological symptoms at the time of discharge were hemiparesis (69/164, 42%), facial palsy (24/164, 15%) and speech disturbance (19/164, 12%). An overview of the age-specific short-term outcomes is provided in Table 5.

Two children (1%) died during the acute phase (day 1 and day 3 after stroke, respectively). One child suffered the stroke as a complication of cardiac surgery (ASD closure) with a bilateral occlusion of the middle cerebral artery, left-sided occlusion of the internal carotid artery and a cerebral edema. Etiology of the stroke in the other child was an acute myeloid leukemia with hyperleukocytosis (196.000 per microliter) leading to a thrombosis of both middle cerebral arteries, the left carotid artery and the anterior cerebral artery. On day 3, the child developed raising intracranial pressure and a brainstem herniation.

Two children died in the post-acute phase, but not because of the arterial ischemic stroke but the severe underlying disease (rupture of an infectious aortic aneurysm and dilatative cardiomyopathy, respectively).

Information about the setting of follow-up care was provided for $n=131$ children. The majority 72/131 (55%) was discharged home with an ambulant follow-up, whereas 59/131 (45%) children were transferred to a rehabilitation clinic. The latter group had significantly more often a

Table 3 Prevalence of risk factors in detail in children with AIS ($n=164$). Some children presented with more than one risk factor within a risk factor category

Risk factor category	In total	As an isolated risk factor category		In total	As an isolated risk factor
Cardiac	47	22	Congenital / Acquired heart disease	25	9
			Patent foramen ovale	15	7
			Endocarditis	2	1
			Previous cardiac surgery / catheterization	4	–
			Arrhythmia	–	–
			Other	7	2
Prothrombotic state	56	15	Protein C deficiency	13	1
			Protein S deficiency	11	1
			Prothrombin mutation (G20210A)	2	–
			Factor V Leiden (G1691A)	9	1
			MTHFR (C677T)		
			Homozygous	2	1
			Heterozygous + hyperhomocysteinemia	2	1
			elevated Lipoprotein (a)	18	5
			Antithrombin deficiency	4	–
			Increased factor VIII	18	2
Arteriopathy	31	9	Focal cerebral arteriopathy	–	–
			Primary CNS-vasculitis	3	–
			Para-/postinfectious vasculitis	5	–
			Arterial dissection	11	3
			Moyamoya disease	7	3
			Fibromuscular dysplasia	–	–
			Systemic lupus erythematodes	2	1
			Other	5	2
Acute systemic	19	4	Infectious disease (varicella, borrelia burgdorferi, mycoplasma pneumonia, enterovirus, parvovirus, other)	19	4
Hemato oncological	15	4	Sickle cell disease	2	1
			Hemolytic anemia	–	–
			Iron deficiency anemia	1	–
			Other	12	3
Metabolic	3	–	Mitochondriopathy	3	–
			M. Fabry	–	–
			Homocysteinuria	–	–
			CDG syndrome	–	–
			Other	–	–
Chronic head and neck disorders	12	8	Brain tumor	–	–
			Aneurysm	3	2
			Arterio-venous malformation	3	2
			Migraine	7	4

Table 3 (continued)

Risk factor category	In total	As an isolated risk factor category		In total	As an isolated risk factor
Other	13	4	Connective tissue disorders		
			Ehlers-Danlos syndrome	–	–
			Marfan syndrome	–	–
			Other	1	1
			Genetic disorders		
			Trisomy 21	4	–
			Other	2	–
			Previous brain surgery	–	–
			Trauma	5	3
			Other	1	–

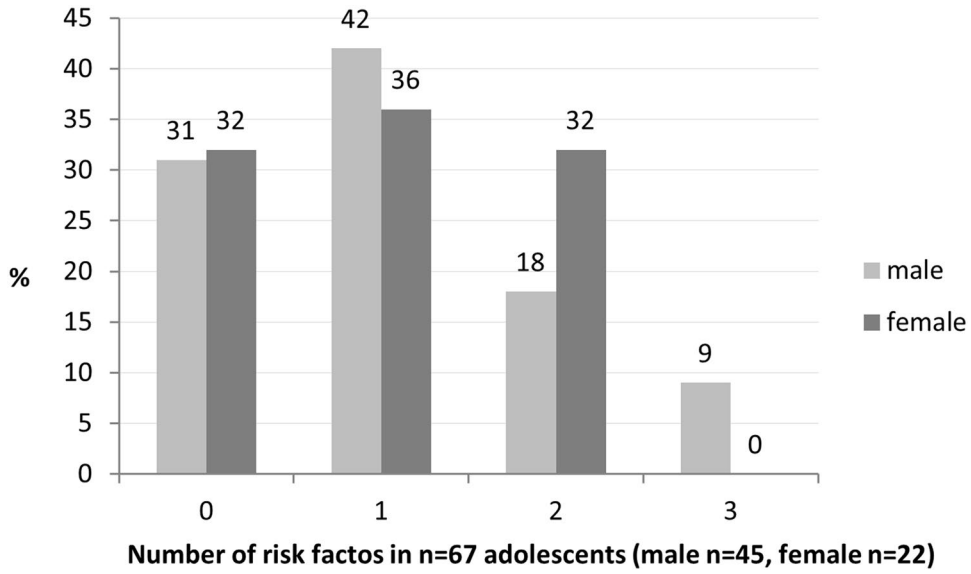

Fig. 2 Number of risk factors in female and male adolescents (≥ 12 years, $n = 67$)

hemiparesis compared to the children which were discharged home (72% vs 28%; $p < 0.0001$).

Discussion

Childhood AIS is a potentially life-threatening event which requires early diagnosis and adequate treatment based on underlying risk factors. Minimizing the risk for recurrent stroke episodes and prioritizing the child's neurological and psychological sequelae is important for the child's integration into its educational, eventual professional and social environment. Our study provides population-based data of childhood AIS and reflects the current medical care situation for children with stroke in Germany. The results regarding age distribution, clinical presentation, risk factors, hyperacute treatment, and short-term outcomes are confirming the previous reports on childhood AIS in most aspects [2, 9–11]. Some points require commentary.

Clinical presentation

The time delay in diagnoses of childhood strokes, reported to be as high as a median interval of 23 h from symptom onset to diagnosis, is a well-known barrier in childhood stroke care, which may prevent time-critical treatments such as thrombolysis or mechanical thrombectomy [7, 12, 13]. The lack of awareness for childhood stroke, the long list of more common, stroke-mimicking conditions, as well as insufficient pediatric stroke codes in hospitals with

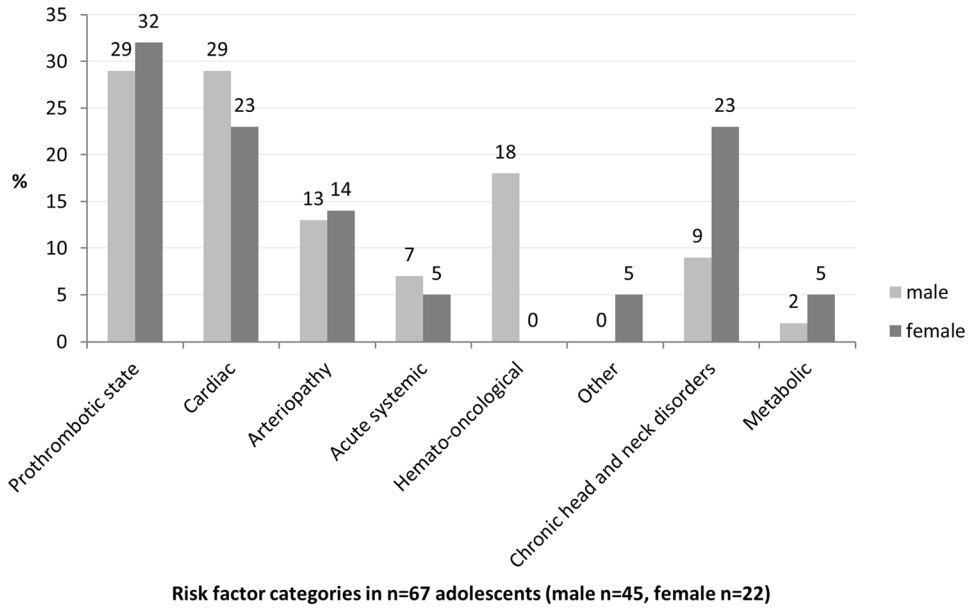

Fig. 3 Risk factor categories in female and male adolescents (≥ 12 years, $n=67$)

Table 4 Affected vessels in children with AIS ($n=110$)

Affected vessel	*N* (total) ($N=110$)	*N* (only one vessel affected) (N = 86)
Middle cerebral artery	75	54
Posterior cerebral artery	20	13
Anterior cerebral artery	15	4
Internal carotid artery	11	5
Cerebellar artery	5	4
Aa. lenticulostriatae	4	2
Basilar artery	2	1
Aa. thalamoperforantes	2	2
A. choroidea ant	2	1
External carotid artery	1	–

delays in proper neuroimaging may be mainly responsible for this unsatisfactory situation. Apart from increasing awareness, there should be considerable effort invested into improving clinical pathways. The evaluation of adult stroke recognition tools in childhood stroke, such as the FAST test (Face Arm Speech Time), beFAST test (b = balance, e = eyes) and the ROSIER scale (Recognition of Stroke in the Emergency Room), as well as ongoing research on how to differentiate stroke from stroke-mimicking conditions in the emergency room, may improve quick diagnosis and treatment [6, 14–21].

The results of our study confirm that nonspecific symptoms such as headache or vomiting and seizures may complicate the diagnosis of childhood stroke. However, the most common presenting symptom, independent of age, is an acute focal neurological deficit. In school-aged children and adolescents, it is worth highlighting that 104/108 children (96%) presented with a clinical symptom listed in the extended FAST Test, the beFAST test (1 child presented with paresthesia only). In adults, the

Table 5 Age-specific short-term outcomes

	Total (n=164)	< 1 year (N=14)	1–5 years ($n=42$)	5–12 years ($N=41$)	12–18 years ($N=67$)	p value
Death	4 (2%)	–	3 (7%)	1 (2%)	–	
Diagnosis at discharge						
Hemiparesis	69 (42%)	7 (50%)	20 (48%)	23 (56%)	19 (28%)	0.0222
Facial palsy	24 (15%)	2 (14%)	7 (17%)	10 (24%)	5 (8%)	0.0883
Speech disturbance	19 (12%)	–	5 (10%)	7 (17%)	7 (10%)	0.4255
Seizures	11 (7%)	1 (7%)	8 (19%)	–	2 (3%)	0.0024
Cerebellar symptoms	6 (4%)	–	3 (7%)	1 (2%)	2 (3%)	0.6129
Visual disturbance	4 (2%)	–	2 (5%)	1 (2%)	1 (2%)	0.8689

beFAST test was shown to be more sensitive than the FAST test in detecting ischemic stroke [14]. These data should encourage paramedics, nurses, and pediatricians to use the beFAST test as triage test for pediatric patients in the emergency room. Unfortunately, pediatricians in non-English speaking countries seem to not be very familiar with this test. Data show that only 27% of pediatricians participating in a survey in Bavaria/Germany were able to correctly explain the meaning of the acronym FAST, and 38% have not heard of the FAST test yet [3]. However, it is to emphasize that the (be)FAST is only a recognition tool for arterial ischemic stroke, not for hemorrhagic stroke. As hemorrhagic stroke in childhood is almost as common as ischemic stroke, the development of pediatric stroke recognition tools should also provide basic information about the clinical presentation of children with intracranial bleeding—severe headache, vomiting, and altered level of consciousness [16]. The Munich Pediatric Stroke Working Group distributed pocket cards (MERCS—Munich Early Recognition of Childhood Stroke) highlighting leading symptoms for both stroke types on the front and back of the pocket card and provided teaching lessons for nurses and pediatricians. The MERCS card can be downloaded as a supplemental material.

With respect to standardized clinical examination tools in childhood stroke, such as the Pediatric NIH Stroke Scale (PedNIHSS) and the Pediatric Stroke Outcome Measure (PSOM), our data show that these are barely used in Germany (information on: PedNIHSS 13/164, PSOM 3/164). Further training sessions will have to focus on these neurological examination tools which are not only the clinical standard in the acute and follow-up examination of children with stroke, but also necessary for collecting comparable data in childhood stroke research [12, 22–24].

We understand it as a genuine task of pediatric societies with all their subspecialities to implement (obligatory) training sessions for early recognition of childhood stroke (beFAST) as well as standardizing neurological examination in acute care phase (PedNIHSS) and long-term follow-up (PSOM).

Risk factors

In the present study, prothrombotic states (39%), cardiac diseases (29%) and arteriopathies (19%) were top of a long list of presumed risk factors for childhood AIS. It is noteworthy that there was significant variance in the proportion of prothrombotic states in different reports of pre-existing conditions in childhood AIS [9, 10, 25–27]. Differences in access to laboratory testing in different countries, as well as higher prevalence of some prothrombotic risk factor in Caucasians (f.e. Factor V Leiden Mutation) could be a reason for this variability.

There is an ongoing research interest in the role of arteriopathies in childhood stroke and some studies consider arteriopathies to be the most common cause [9, 28–31]. Especially, focal cerebral arteriopathies, an unilateral arteriopathy without progression after 3–6 months, seems to be responsible for a remarkable proportion of childhood strokes [32, 33]. There is no good explanation for why, over a three-year period, no focal cerebral arteriopathy was reported in our cohort, or for why the proportion of para-/postinfectious vasculitis was so low in general. As our study design did not include validation measures of neuroimaging results, we cannot exclude that some arteriopathies remained undetected.

Childhood stroke is known to be a multiple-risk disease, meaning that the presence and the interaction of different factors may lead to an ischemic event. In the present study, 40% of children showed at least 2 risk factors, 34% presented with one risk factor, and in 26% of the patient's stroke was classified as cryptogenic. The causal role of some isolated risk factors in childhood stroke, for example, the presence of an isolated patent foramen ovale, high Lipoprotein (a) levels, or migraine, has not yet been fully clarified.

For the prevention of recurrent strokes, large trials (CLOSE and REDUCE trials) showed the benefits of a PFO closure in adult patients (< 60 years) with a PFO and a cryptogenic stroke, compared to antiplatelet therapy alone [34]. Some additional criteria for the PFO as large size, or significant right to left shunt (RTLS), as well as a thorough and complete diagnostic work-up justifying the diagnosis of cryptogenic stroke may aid in selecting appropriate candidates for PFO closure. In children, where the list of risk factors and the possible combinations may be even more complex, paradoxical embolism from a PFO as a single cause of stroke remains a diagnosis reached by exclusionary process [35]. In the present study, a PFO as an isolated risk factor was detected in 9 children. However, unfortunately, these case report forms did not provide any additional information on the size of the defect, a significant RTLS, atrial septal aneurysm, or whether the diagnosis of the PFO in the child with stroke resulted in a PFO closure.

In 5 children, high Lipoprotein (a) [Lp (a)] levels were reported as single risk factors. Elevated Lp (a) levels are a known adult cardiovascular risk factor, but there are only limited data regarding childhood stroke [36–38]. While a German study identified an isolated Lp (a) elevation (> 30 mg/dl) as a risk factor for spontaneous ischemic stroke in children, these results could not be confirmed by other studies, which only found high Lp (a) levels as a mild prognostic factor for recurrent strokes [39–42].

Migraine with aura seems to be associated with an increased risk for ischemic stroke in adults and adolescent migraineurs aged 12–18 years, but not in the overall

pediatric population [43–45]. Interestingly, a recently published study described migraine with visual aura as being associated with an increased risk for atrial fibrillation, which may be one explanation for the increased risk for ischemic stroke in this population [46]. These results and their relevance for pediatric patients have to be confirmed in further studies.

Our data show incidence of AIS peaks in infants, very young children and adolescence without significant differences in risk factor categories. Our results could not support the hypothesis that infants and toddlers are at a higher risk of infectious diseases and therefor at higher risk for para-infectious vasculopathies leading to an ischemic stroke [47–49]. Indeed, our case report form may have missed some mild upper respiratory tract infections up to one week before the stroke event, but considering the results of other studies, pediatricians were expected to report a higher proportion of vasculopathies in stroke patients in the younger age group.

With respect to the incidence peak in adolescence, our data again did not show an age-dependency of risk factors. Furthermore, we failed to explain the highly significant male predominance in this age group, regarding risk factor category and number of risk factors. Besides a possible neuroprotective effect of estrogen or the influence of endogenous testosterone, further risk factors discussed in ischemic stroke in young adults (defined as patients less than 50 years) should be investigated in further studies [50–52]. As only three females in this age group took contraceptives and we have no information whether the contraceptives were estrogen containing, our data cannot contribute to the discussion whether estrogen containing contraceptives increase the risk of stroke in adolescents with additional prothrombotic risk factors or with migraine.

In addition to known risk factors in childhood and young adult stroke, such as cardioembolic risk factors, inflammatory and non-inflammatory vasculopathies, and spontaneous and traumatic cervicocerebral artery dissections, some studies also place vascular risk factors in general in the focus of interest [53]. A large Finnish study compared 918 ischemic stroke patients between 25 and 49 years old to 1392 healthy controls [54] The highest population attributable risk factors were found to be smoking, hypertension, low HDL-C, cardiovascular disease (CVD), type 1 diabetes mellitus, a family history of stroke, type 2 diabetes mellitus (T2D), and atrial fibrillation. CVD, low HDL-C, T2D, a family history of stroke and hypertension emerged as significant risk factors only in men. A Germany nationwide case–control study focused on potentially modifiable cardiovascular/"lifestyle" risk factors in young adults aged 18–55 years [55]. Low physical activity, hypertension, heavy episodic alcohol consumption, smoking, and overweight/obesity contributed significantly to the risk of ischemic stroke. Substance abuse is a further important risk factor in stroke in young adults [56]. Whereas cocaine abuse is known to increase the risk for a stroke significantly, studies show controversial results regarding the potential role of cannabis use in the etiology of stroke.

As risk factors of childhood stroke are also of (research) interest in young adults, may be advisable to combine research activities in adolescents and young adults for a mutual exchange of knowledge of probable risk factor profiles [57].

Follow-up

After an optimized treatment in the acute phase, rehabilitation and thorough follow-up of children with stroke is necessary for the best possible long-term outcome and participation in daily life. Recently, guidelines and recommendations for the acute treatment and criteria for primary childhood stroke centers have been published in different countries [58, 59]. Same efforts should be invested into standardizing long-term care and follow-up. Rehabilitation clinics offer treatment by multidisciplinary personnel to children after stroke, including therapists, psychologists, and social workers. Fortunately, our data show that children with hemiparesis after stroke are significantly more often transferred to a rehabilitation clinic than being discharged home. However, patients being discharged home after acute care phase with no or only minor neurological deficits, as the majority of children in our cohort (72/131 children), are especially at high risk for being lost to follow-up. Life-changing sequela such as fatigue, attention deficits, cognitive decline, and psychiatric comorbidities may be overlooked. Therefore, special follow-up settings and personnel are needed. In Germany, so-called social pediatric centers (SPZ) provide specialized multi-professional, interdisciplinary treatment in an outpatient setting, and caring about all bio-psycho-social aspects. These SPZ should be the preferred long-term follow-up setting for children and adolescents after stroke. In addition, introducing a specialized case manager to the family in the acute treatment phase, who provides care to the patient and the family within the first months of recovery and organizes the follow-up appointments, seems to be a solution currently being implemented and evaluated in adult stroke medicine in Germany [60, 61]. Further prospective studies or registry-based data are required to capture all children with childhood arterial ischemic stroke to describe accurately long-term outcomes and how these outcomes are influenced by underlying aetiology, acute, and rehabilitative treatment.

Strength and limitations of the study

Strength of this study is its prospective design, population-based approach, and the relatively large study population.

Underreporting may be a significant limitation (ESPED is a voluntary reporting system) which may explain the lower estimated incidences for childhood stroke in Germany compared to other countries (0.41/100,000 per year compared to 1.25–13/100,000 per year) [4, 10, 62]. The fact that in Germany, adolescents with stroke are also admitted to adult stroke units, and in general, more than 35% of children (< 15 years) are not treated in children`s hospitals, may also contribute to the lower incidences for childhood stroke as only children`s hospitals and pediatric departments are reporting to ESPED [63].

However, it is improbable that underreporting had a significant influence on the described results. The study design did not provide predetermined investigation protocols; therefore, analysis of risk factors was limited. Though inquired about through the questionnaire, we unfortunately did not receive sufficient information about the completeness or the extent of laboratory or imaging investigations in different hospitals. Furthermore, images were not centrally validated and we did not receive any information on how often vessel wall imaging was performed. As mentioned above, it is possible that some etiological hints were overlooked, and for example, arteriopathies as underlying etiology were underreported.

Conclusions

There has been some effort to improve diagnostic accuracy in childhood stroke in the emergency department, and the effectiveness of different adult stroke recognition tools has been evaluated for childhood stroke recognition with somewhat unsatisfying results. Well aware that it often remains a challenge to distinguish stroke from stroke-mimicking conditions in the emergency room, we would still like to encourage pediatricians to use the beFAST test. In our cohort, 96% of all school-aged children and adolescents (6–18 years) showed at least one symptom listed in the beFAST test. Furthermore, being familiar with the beFAST test will undoubtedly increase awareness for childhood stroke, and, therefore, hopefully help to shorten the time to diagnosis. Nevertheless, one should keep in mind that hemorrhagic stroke in children is almost as common as ischemic stroke. Clinical symptoms of hemorrhagic stroke are not covered by the beFAST test, and therefore, the development of child-specific recognition tools of stroke should provide information of both stroke types, ischemic events and intracranial bleeding.

With respect to the low percentages of arteriopathies in general, and the absence of focal cerebral arteriopathy in particular in our cohort, standardized vascular and vessel wall imaging protocols analyzed by experienced neuroradiologists are necessary.

Considering the higher stroke incidence in (male) adolescents and given the fact that a relevant number of adolescents are already treated at adult stroke units, it is advisable to combine research activities in adolescents and young adults for a mutual exchange of knowledge of risk factor profiles, treatment options, and outcomes. In this context, research should also include the role of endocrinological aspects and modifiable cardiovascular and stroke risk factors such as obesity, hypertension, heavy episodic alcohol consumption, and tobacco or drug abuse.

As a remarkable proportion of children with stroke can be discharged home from the acute care hospital, it is necessary to implement standardized follow-up protocols and to provide sufficient support for the affected families. Especially, children with no obvious neurological deficit on the side of the motor system are at a great risk to be lost to follow-up, and therefore, later, in life restricting sequelae such as fatigue, cognition decline, or social problems, which may not to be overlooked and/or misattributed.

Acknowledgements The authors thank all pediatricians reporting to ESPED.

Funding Building up the database was financially supported by Friedrich-Baur-Stiftung, München.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards statement The study was approved by the ethics committee of the Medical Faculty of the Ludwig-Maximilians-University Munich, Number 42-15 (05-04-2015) and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Bhogal P, Andersson T, Maus V, Mpotsaris A, Yeo L (2018) Mechanical thrombectomy-a brief review of a revolutionary new treatment for thromboembolic stroke. Clin Neuroradiol. https://doi.org/10.1007/s00062-018-0692-2
2. Bigi S, Dulcey A, Gralla J, Bernasconi C, Melliger A, Datta AN, Arnold M, Kaesmacher J, Fluss J, Hackenberg A, Maier O, Weber J, Poloni C, Fischer U, Steinlin M (2018) Feasibility, safety, and outcome of recanalization treatment in childhood stroke. Ann Neurol 83(6):1125–1132. https://doi.org/10.1002/ana.25242
3. Bonfert MV, Badura K, Gerstl J, Borggraefe I, Heinen F, Schroeder S, Olivieri M, Weinberger R, Landgraf MN, Vill K, Tacke M, Berweck S, Reiter K, Hoffmann F, Nicolai T, Gerstl L (2018) Childhood stroke: awareness, interest, and knowledge

among the pediatric community. Front Pediatr 6:182. https://doi.org/10.3389/fped.2018.00182
4. Fullerton HJ, Wu YW, Zhao S, Johnston SC (2003) Risk of stroke in children: ethnic and gender disparities. Neurology 61(2):189–194
5. Gerstl L, Bonfert MV, Nicolai T, Dieterich M, Adamczyk C, Heinen F, Olivieri M, Steinlin M (2017) Childhood stroke: what are the special features of childhood stroke? Nervenarzt 88(12):1367–1376. https://doi.org/10.1007/s00115-017-0435-7
6. Mackay MT, Yock-Corrales A, Churilov L, Monagle P, Donnan GA, Babl FE (2016) Differentiating childhood stroke from mimics in the Emergency Department. Stroke 47(10):2476–2481. https://doi.org/10.1161/STROKEAHA.116.014179
7. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T, Parker AP, Wassmer E, Wraige E, Amin S, Edwards HB, O'Callaghan FJ (2015) Diagnostic delays in paediatric stroke. J Neurol Neurosurg Psychiatry 86(8):917–921. https://doi.org/10.1136/jnnp-2014-309188
8. Statistisches Bundesamt Deutschland (2019) GENESIS-Online: Bevölkerung: Deutschland, Stichtag, Altersjahre, Nationalität/Geschlecht/Familienstand; Ergebnis—12411-0006. https://www-genesis.destatis.de. Accessed 4 February 2019
9. Mackay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA, Ganesan V, International Pediatric Stroke Study G (2011) Arterial ischemic stroke risk factors: the international pediatric stroke study. Ann Neurol 69(1):130–140. https://doi.org/10.1002/ana.22224
10. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T, Parker AP, Wassmer E, Wraige E, Amin S, Edwards HB, Tilling K, O'Callaghan FJ (2014) Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. Lancet Neurol 13(1):35–43. https://doi.org/10.1016/S1474-4422(13)70290-4
11. Steinlin M, Pfister I, Pavlovic J, Everts R, Boltshauser E, Capone Mori A, Gubser Mercati D, Hanggeli CA, Keller E, Luetschg J, Marcoz J, Ramelli GP, Roulet Perez E, Schmitt-Mechelke T, Weissert M, Societies Swiss, of Paediatric N, Neonatology, (2005) The first three years of the Swiss Neuropaediatric Stroke Registry (SNPSR): a population-based study of incidence, symptoms and risk factors. Neuropediatrics 36(2):90–97. https://doi.org/10.1055/s-2005-837658
12. Lehman LL, Beslow LA, Steinlin M, Kossorotoff M, Mackay MT (2019) What will improve pediatric acute stroke care? Stroke 50(2):249–256. https://doi.org/10.1161/STROKEAHA.118.022881
13. Martin C, von Elm E, El-Koussy M, Boltshauser E, Steinlin M, Swiss Neuropediatric Stroke Registry study g (2011) Delayed diagnosis of acute ischemic stroke in children—a registry-based study in Switzerland. Swiss Med Wkly 141:w13281. https://doi.org/10.4414/smw.2011.13281
14. Aroor S, Singh R, Goldstein LB (2017) BE-FAST (Balance, Eyes, Face, Arm, Speech, Time): reducing the proportion of strokes missed using the FAST Mnemonic. Stroke 48(2):479–481. https://doi.org/10.1161/STROKEAHA.116.015169
15. Mackay MT, Chua ZK, Lee M, Yock-Corrales A, Churilov L, Monagle P, Donnan GA, Babl FE (2014) Stroke and nonstroke brain attacks in children. Neurology 82(16):1434–1440. https://doi.org/10.1212/WNL.0000000000000343
16. Mackay MT, Churilov L, Donnan GA, Babl FE, Monagle P (2016) Performance of bedside stroke recognition tools in discriminating childhood stroke from mimics. Neurology 86(23):2154–2161. https://doi.org/10.1212/WNL.0000000000002736
17. Mackay MT, Lee M, Yock-Corrales A, Churilov L, Donnan GA, Monagle P, Babl FE (2018) Differentiating arterial ischaemic stroke from migraine in the paediatric emergency department. Dev Med Child Neurol 60(11):1117–1122. https://doi.org/10.1111/dmcn.13772
18. Mackay MT, Monagle P, Babl FE (2016) Brain attacks and stroke in children. J Paediatr Child Health 52(2):158–163. https://doi.org/10.1111/jpc.13086
19. Neville K, Lo W (2016) Sensitivity and specificity of an adult stroke screening tool in childhood ischemic stroke. Pediatr Neurol 58:53–56. https://doi.org/10.1016/j.pediatrneurol.2016.02.001
20. Yock-Corrales A, Babl FE, Mosley IT, Mackay MT (2011) Can the FAST and ROSIER adult stroke recognition tools be applied to confirmed childhood arterial ischemic stroke? BMC Pediatr 11:93. https://doi.org/10.1186/1471-2431-11-93
21. Yock-Corrales A, Varela-Bulgarelli F, Barboza C, Gutierrez-Mata A, Mackay MT, Babl F (2016) Presentation of acute childhood stroke in a Tertiary Pediatric Emergency Department. Pediatr Emerg Care. https://doi.org/10.1097/PEC.0000000000000918
22. Bulder MM, Hellmann PM, van Nieuwenhuizen O, Kappelle LJ, Klijn CJ, Braun KP (2011) Measuring outcome after arterial ischemic stroke in childhood with two different instruments. Cerebrovasc Dis 32(5):463–470. https://doi.org/10.1159/000332087
23. Cooper AN, Anderson V, Hearps S, Greenham M, Hunt RW, Mackay MT, Monagle P, Gordon AL (2018) The Pediatric stroke outcome measure: a predictor of outcome following arterial ischemic stroke. Neurology 90(5):e365–e372. https://doi.org/10.1212/WNL.0000000000004906
24. Ichord RN, Bastian R, Abraham L, Askalan R, Benedict S, Bernard TJ, Beslow L, Deveber G, Dowling M, Friedman N, Fullerton H, Jordan L, Kan L, Kirton A, Amlie-Lefond C, Licht D, Lo W, McClure C, Pavlakis S, Smith SE, Tan M, Kasner S, Jawad AF (2011) Interrater reliability of the Pediatric National Institutes of Health Stroke Scale (PedNIHSS) in a multicenter study. Stroke 42(3):613–617. https://doi.org/10.1161/STROKEAHA.110.607192
25. Chan AK, deVeber G (2000) Prothrombotic disorders and ischemic stroke in children. Semin Pediatr Neurol 7(4):301–308
26. Deng Y, Wang Y, Yang W, Yu Y, Xu J, Wang Y, Gao B (2015) Risk factors and imaging characteristics of childhood stroke in china. J Child Neurol 30(3):339–343. https://doi.org/10.1177/0883073814538667
27. Zadro R, Herak DC (2012) Inherited prothrombotic risk factors in children with first ischemic stroke. Biochem Med 22(3):298–310
28. Amlie-Lefond C, Bernard TJ, Sebire G, Friedman NR, Heyer GL, Lerner NB, DeVeber G, Fullerton HJ, International Pediatric Stroke Study G (2009) Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the international pediatric stroke study. Circulation 119(10):1417–1423. https://doi.org/10.1161/CIRCULATIONAHA.108.806307
29. Braun KP, Bulder MM, Chabrier S, Kirkham FJ, Uiterwaal CS, Tardieu M, Sebire G (2009) The course and outcome of unilateral intracranial arteriopathy in 79 children with ischaemic stroke. Brain 132(Pt 2):544–557. https://doi.org/10.1093/brain/awn313
30. Kirton A, deVeber G (2015) Paediatric stroke: pressing issues and promising directions. Lancet Neurol 14(1):92–102. https://doi.org/10.1016/S1474-4422(14)70227-3
31. Wintermark M, Hills NK, deVeber GA, Barkovich AJ, Elkind MS, Sear K, Zhu G, Leiva-Salinas C, Hou Q, Dowling MM, Bernard TJ, Friedman NR, Ichord RN, Fullerton HJ, Investigators V (2014) Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the vascular effects of infection in pediatric stroke study. Stroke 45(12):3597–3605. https://doi.org/10.1161/STROKEAHA.114.007404
32. Steinlin M, Bigi S, Stojanovski B, Gajera J, Regenyi M, El-Koussy M, Mackay MT (2017) Focal cerebral arteriopathy: do steroids improve outcome? Stroke. https://doi.org/10.1161/STROKEAHA.117.016818

33. Yeon JY, Shin HJ, Seol HJ, Kim JS, Hong SC (2014) Unilateral intracranial arteriopathy in pediatric stroke: course, outcome, and prediction of reversible arteriopathy. Stroke 45(4):1173–1176. https://doi.org/10.1161/STROKEAHA.113.004125
34. Kottoor SJ, Arora RR (2018) Cryptogenic stroke: to close a patent Foramen Ovale or not to close? J Cent Nerv Syst Dis 10:1179573518819476. https://doi.org/10.1177/1179573518819476
35. Khan R, Chan AK, Mondal TK, Paes BA, Thrombosis Hemostasis in Newborns G (2016) Patent foramen ovale and stroke in childhood: a systematic review of the literature. Eur J Paediatr Neurol 20(4):500–511. https://doi.org/10.1016/j.ejpn.2016.04.012
36. Sultan S, Dowling M, Kirton A, DeVeber G, Linds A, Elkind MSV, Investigators I (2018) Dyslipidemia in children with arterial ischemic stroke: prevalence and risk factors. Pediatr Neurol 78:46–54. https://doi.org/10.1016/j.pediatrneurol.2017.09.019
37. Sultan SM, Schupf N, Dowling MM, Deveber GA, Kirton A, Elkind MS (2014) Review of lipid and lipoprotein(a) abnormalities in childhood arterial ischemic stroke. Int J Stroke 9(1):79–87. https://doi.org/10.1111/ijs.12136
38. Willeit P, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, Xu Q, Mayr A, Willeit J, Tsimikas S (2014) Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. J Am Coll Cardiol 64(9):851–860. https://doi.org/10.1016/j.jacc.2014.03.061
39. deVeber G, Kirkham F, Shannon K, Brandao L, Strater R, Kenet G, Clausnizer H, Moharir M, Kausch M, Askalan R, MacGregor D, Stoll M, Torge A, Dlamini N, Ganesan V, Prengler M, Singh J, Nowak-Gottl U (2019) Recurrent stroke: the role of thrombophilia in a large international pediatric stroke population. Haematologica. https://doi.org/10.3324/haematol.2018.211433
40. Goldenberg NA, Bernard TJ, Hillhouse J, Armstrong-Wells J, Galinkin J, Knapp-Clevenger R, Jacobson L, Marcovina SM, Manco-Johnson MJ (2013) Elevated lipoprotein (a), small apolipoprotein (a), and the risk of arterial ischemic stroke in North American children. Haematologica 98(5):802–807. https://doi.org/10.3324/haematol.2012.073833
41. Nowak-Gottl U, Strater R, Heinecke A, Junker R, Koch HG, Schuierer G, von Eckardstein A (1999) Lipoprotein (a) and genetic polymorphisms of clotting factor V, prothrombin, and methylenetetrahydrofolate reductase are risk factors of spontaneous ischemic stroke in childhood. Blood 94(11):3678–3682
42. Strater R, Becker S, von Eckardstein A, Heinecke A, Gutsche S, Junker R, Kurnik K, Schobess R, Nowak-Gottl U (2002) Prospective assessment of risk factors for recurrent stroke during childhood–a 5-year follow-up study. Lancet 360(9345):1540–1545. https://doi.org/10.1016/S0140-6736(02)11520-0
43. Androulakis XM, Kodumuri N, Giamberardino LD, Rosamond WD, Gottesman RF, Yim E, Sen S (2016) Ischemic stroke subtypes and migraine with visual aura in the ARIC study. Neurology 87(24):2527–2532. https://doi.org/10.1212/WNL.0000000000003428
44. Gelfand AA, Fullerton HJ, Jacobson A, Sidney S, Goadsby PJ, Kurth T, Pressman A (2015) Is migraine a risk factor for pediatric stroke? Cephalalgia 35(14):1252–1260. https://doi.org/10.1177/0333102415576222
45. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T (2009) Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 339:b3914. https://doi.org/10.1136/bmj.b3914
46. Sen S, Androulakis XM, Duda V, Alonso A, Chen LY, Soliman EZ, Magnani J, Trivedi T, Merchant AT, Gottesman RF, Rosamond WD (2018) Migraine with visual aura is a risk factor for incident atrial fibrillation: a cohort study. Neurology 91(24):e2202–e2210. https://doi.org/10.1212/WNL.0000000000006650
47. Elkind MS, Hills NK, Glaser CA, Lo WD, Amlie-Lefond C, Dlamini N, Kneen R, Hod EA, Wintermark M, deVeber GA, Fullerton HJ, Investigators* V, (2016) herpesvirus infections and childhood arterial ischemic stroke: results of the VIPS study. Circulation 133(8):732–741. https://doi.org/10.1161/CIRCULATIONAHA.115.018595
48. Fullerton HJ, Hills NK, Elkind MS, Dowling MM, Wintermark M, Glaser CA, Tan M, Rivkin MJ, Titomanlio L, Barkovich AJ, deVeber GA, Investigators V (2015) Infection, vaccination, and childhood arterial ischemic stroke: results of the VIPS study. Neurology 85(17):1459–1466. https://doi.org/10.1212/WNL.0000000000002065
49. Fullerton HJ, Luna JM, Wintermark M, Hills NK, Tokarz R, Li Y, Glaser C, DeVeber GA, Lipkin WI, Elkind MSV, Investigators* V, (2017) Parvovirus B19 infection in children with arterial ischemic stroke. Stroke 48(10):2875–2877. https://doi.org/10.1161/STROKEAHA.117.018272
50. Czlonkowska A, Ciesielska A, Gromadzka G, Kurkowska-Jastrzebska I (2006) Gender differences in neurological disease: role of estrogens and cytokines. Endocrine 29(2):243–256. https://doi.org/10.1385/ENDO:29:2:243
51. Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G, International Pediatric Stroke Study G (2009) Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. Stroke 40(1):52–57. https://doi.org/10.1161/STROKEAHA.108.521203
52. Normann S, de Veber G, Fobker M, Langer C, Kenet G, Bernard TJ, Fiedler B, Strater R, Goldenberg NA, Nowak-Gottl U (2009) Role of endogenous testosterone concentration in pediatric stroke. Ann Neurol 66(6):754–758. https://doi.org/10.1002/ana.21840
53. Stack CA, Cole JW (2018) Ischemic stroke in young adults. Curr Opin Cardiol 33(6):594–604. https://doi.org/10.1097/HCO.0000000000000564
54. Kivioja R, Pietila A, Martinez-Majander N, Gordin D, Havulinna AS, Salomaa V, Aarnio K, Curtze S, Leiviska J, Rodriguez-Pardo J, Surakka I, Kaste M, Tatlisumak T, Putaala J (2018) Risk factors for early-onset ischemic stroke: a case-control study. J Am Heart Assoc 7(21):e009774. https://doi.org/10.1161/JAHA.118.009774
55. Aigner A, Grittner U, Rolfs A, Norrving B, Siegerink B, Busch MA (2017) Contribution of established stroke risk factors to the burden of stroke in young adults. Stroke 48(7):1744–1751. https://doi.org/10.1161/STROKEAHA.117.016599
56. Bhatt N, Malik AM, Chaturvedi S (2018) Stroke in young adults: five new things. Neurol Clin Pract 8(6):501–506. https://doi.org/10.1212/CPJ.0000000000000522
57. van Alebeek ME, Arntz RM, Ekker MS, Synhaeve NE, Maaijwee NA, Schoonderwaldt H, van der Vlugt MJ, van Dijk EJ, Rutten-Jacobs LC, de Leeuw FE (2018) Risk factors and mechanisms of stroke in young adults: the FUTURE study. J Cereb Blood Flow Metab 38(9):1631–1641. https://doi.org/10.1177/0271678X17707138
58. Ferriero DM, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, DeBaun MR, deVeber G, Ichord RN, Jordan LC, Massicotte P, Meldau J, Roach ES, Smith ER, American Heart Association Stroke C, Council on C, Stroke N (2019) Management of Stroke in Neonates and Children: A Scientific Statement From the American Heart Association/American Stroke Association. Stroke. https://doi.org/10.1161/STR.0000000000000183
59. Medley TL, Miteff C, Andrews I, Ware T, Cheung M, Monagle P, Mandelstam S, Wray A, Pridmore C, Troedson C, Dale RC, Fahey M, Sinclair A, Walsh P, Stojanovski B, Mackay MT (2018) Australian Clinical Consensus Guideline: The diagnosis and acute management of childhood stroke. Int J Stroke. https://doi.org/10.1177/1747493018799958
60. Barlinn J, Barlinn K, Helbig U, Siepmann T, Pallesen LP, Urban H, Putz V, Schmitt J, Reichmann H, Bodechtel U (2016)

Organized post-stroke care through case management on the basis of a standardized treatment pathway : results of a single-centre pilot study. Nervenarzt 87(8):860–869. https://doi.org/10.1007/s00115-016-0100-6

61. Bodechtel U, Barlinn K, Helbig U, Arnold K, Siepmann T, Pallesen LP, Puetz V, Reichmann H, Schmitt J, Kepplinger J (2016) The stroke east Saxony pilot project for organized post-stroke care: a case-control study. Brain Behav 6(5):e00455. https://doi.org/10.1002/brb3.455
62. Lynch JK, Hirtz DG, DeVeber G, Nelson KB (2002) Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. Pediatrics 109(1):116–123
63. Bundesamt für gesundheitliche Aufklärung (2019) Welches Krankenhaus ist das Richtige? https://www.kindergesundheit-info.de/themen/krankes-kind/im-krankheitsfall/krankenhaus10/. Accessed 18 Mar 2019