

Theme Issue Article

Arterial ischaemic stroke in children

Review of the literature and strategies for future stroke studies

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Summary

Conditions associated with arterial ischaemic stroke in children include a great variety of diseases and triggers such as congenital heart malformations, sickle cell disease, infections and vasculopathies, although up to 50% are cryptogenic. An abnormal vascular status can be demonstrated by vascular imaging in up to 80% of children with ischaemic stroke, and case control studies demonstrate an association between ischaemic stroke in children and hereditary prothrombotic risk factors and infections such as Varicella. Conventional risk factors such as hyper-

tension and dyslipidaemia may also play a role, and most children have several potential triggers rather than one single cause. This review focuses on clinical presentations, imaging methods, stroke subtypes, underlying conditions including prothrombotic risk factors, outcome and recurrence. Although data from randomised controlled trials, on which clinical practice might be based, are sparse, therapeutic approaches and future research directions are discussed.

Keywords

Pediatric stroke, etiology, risk assessment

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Introduction

Arterial ischaemic stroke is a rare disease, but is being increasingly diagnosed and recognised in childhood. The fact that the available data on this subject are drawn from only a very small number of studies or retrospective case series, explains the great variance in reported etiological risk factors as well as in treatment strategies. Despite the small quantity of published data, the problem is of growing significance in the paediatric population since paediatric ischaemic stroke can nowadays be detected much more efficiently than in the past. Unfortunately, no evidence-based recommendations have been issued to date.

The present review is, therefore, aimed at achieving a consensus statement on a little studied condition. Based on a Medline search with “milestone” paediatric reports (case-control studies or case series) and new literature data up to April 2004, the present review is focused on clinical presentation, underlying diseases, diagnostic imaging and laboratory tools. As a consensus paper, this review might be a step towards more international co-operation, e.g. in the form of essential multi-centre collaborative studies and research into paediatric ischaemic stroke. Therapeutic approaches are briefly discussed as a basis for the development of randomised controlled trials in children with stroke. However, research in this important field needs to continue well into the future.

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Epidemiology and risk factors for paediatric ischaemic stroke

Although stroke in childhood has been recognised for centuries (1), and is at least as common as brain cancer in childhood, historically it has been considered difficult or impossible to treat, and so has received comparatively little attention. The estimated incidence is between 1.29 and 13.0 per 100,000 per year, with half of the events reported presenting as ischaemic

Table 1: Clinical causes and triggers of ischaemic stroke in childhood.

Causes and triggers of ischaemic stroke in childhood
N.B.: - no guarantee of completeness - overlap between diverse subgroups and causes possible
Cryptogenic (idiopathic or unknown)
Cardiac disease:
- Congenital heart disease
- Infectious endocarditis
- Valvular disease
- Cardiomyopathy
- Arrhythmia
Haematological disorders:
- Sickle cell disease
- Inherited prothrombotic risk factors & lipid abnormalities
- Antiphospholipid antibodies
- Lymphoproliferative disorders
Arterial vasculopathy:
- Moyamoya
- Fibromuscular dysplasia
- Transient cerebral arteriopathy
- Para/peri/postinfectious vasculitis (e.g. post-varicella)*
- Takayasu arteriitis
- Systemic lupus erythematosus
Trauma:
- Blunt trauma to posterior pharynx
- Cervical spine rotation/dislocation
- Dissection*
Infections:
- Meningitis
- Diverse viral, bacterial, mycotic infections
- Others (endocarditis, vasculitis)
Drugs:
- Cocaine
- Sympathomimetics
- Oral contraceptives
Surgical interventions:
- Cardiac surgery/catheterisation
- Cerebral angiography
- Extracorporeal membrane oxygenation (ECMO)
Neurocutaneous diseases:
- Neurofibromatosis I
- Sturge Weber and others
Migraine
Metabolic diseases:
- Homocystinuria/ hyperhomocysteinaemia
- MELAS lactic acidosis & stroke-like episodes
- CDG (congenital disorders of glycosylation) syndrome
- Others (OTC deficiency)

strokes (2-6). Predisposing conditions for ischaemic stroke in children include a wide spectrum of underlying diseases such as congenital heart malformations, sickle cell disease, infections, vasculopathies and collagen tissue abnormalities (Table 1; 5, 7-13), but around half of such events occur in children who were previously well (cryptogenic stroke: 10). Vascular imaging of the affected arteries reveals pathological findings in up to 80% of children with ischaemic stroke (14-18). In addition, hypercoagulable states associated with different prothrombotic risk factors also appear to be important (10, 15, 19-42). There is a variety of further possible risk factors for primary and secondary stroke in childhood which require further investigation. In summary, it is becoming increasingly evident that childhood stroke is frequently triggered by multiple risk factors. With regard to the treatment of paediatric ischaemic stroke, appropriate patient management is seriously hampered by the lack of clinical trials (9, 43, 44).

Neonatal ischaemic stroke

One third of all cases of ischaemic stroke reported present during the neonatal period with an estimated incidence of 1 in every 4,000 newborns (34, 45).

The presentation of stroke in neonates may be different from that in older age groups (34, 45). The clinical symptoms are often non-specific, e.g. muscular hypotonia, apnoea or lethargy, with or without focal neurological deficits. In more seriously ill neonates or in neonates with seizures as the most pronounced clinical finding, the diagnosis might be made at an early stage. Neurological signs may appear during the first year of life as motor skills develop (34, 46, 47); however, in many children the diagnosis is made retrospectively in later months, following the presentation of neurological impairments (48).

Triggering factors for ischaemic stroke in newborns differ from those for stroke beyond the neonatal period. Causes are related to age-specific problems and conditions in the pre-, peri- and early post-partal period, e.g. asphyxia, bacterial infections such as meningitis or chorioamnionitis, central line catheters, metabolic disorders in the mother or the child, as well as inherited or acquired prothrombotic risk factors or coagulopathies (28, 34). Despite there being a battery of causes, many cases remain unexplained. In the main group, the pathomechanism of a paradoxical embolism originating from venous thrombus or placental material via the foramen ovale or in children with congenital complex heart malformations is discussed (43, 49, 50).

As a consequence of the non-specific clinical symptoms, neonatal stroke is detected in the acute phase only in rare cases, and no recommendations have been issued to date for acute antithrombotic treatment (48). With respect to the neurological and the neuropsychological late effects reported in the wake of neonatal stroke (51, 52), it may be mandatory to shorten the time

lapsing between stroke event and diagnosis, using neuro-radiological diagnostic approaches in this age group (45), as discussed later in this manuscript. In view of the pathogenesis of neonatal stroke, the possibility of initiating acute phase treatment with heparins in selected cases might be discussed. However, because of the lack of any study in this field, it remains completely unclear whether early diagnosis and early intervention lead to a better prognosis for the affected patients. Thus prospective long-term follow-up studies are urgently recommended to clarify the potential benefits of acute treatment and of secondary stroke prevention.

Overall, the probability of recurrence seems to be small: In a prospective follow-up study of 215 children suffering from neonatal stroke, only 3.3% suffered a second thromboembolic event, either ischaemic stroke or venous thrombosis, the latter primarily in the cerebral sinuses, with a median time of 12 months after first stroke onset (53).

Ischaemic stroke beyond the neonatal period

Clinical presentation at onset

Ischaemic stroke is defined as a focal neurological deficit lasting more than 24 hours with no cause other than that of vascular origin, although transient ischaemic attacks, defined as neurological deficits lasting less than 24 hours, are commonly associated with infarction in children and many series have included these patients. In addition, seizures and decreased levels of consciousness are common presentations of stroke in younger children, particularly in those under four years of age, although a meticulous initial neurological examination reveals focal neurological deficits in most cases. Stroke in later childhood may manifest as hemiplegia, aphasia or altered level of consciousness (54), or as other focal neurological disturbances, e.g. visual and sensory impairment, or ataxia in posterior circulation stroke (55). Headache is commonly associated, and there may also be a clear history of recent infection or trauma (56). A detailed past medical and family history should be taken as these may provide clues to the aetiology.

Metabolic disorders due to stroke, e.g. secondary to mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), ornithine transcarbamylase deficiency (OTC) are relatively rare. There are often clinical clues like persistent vomiting, and neuroimaging usually reveals that the infarcts are not in a typical vascular distribution (9, 11, 58).

Differential diagnostic investigations

Haemorrhage, which may require urgent neurosurgical intervention, must be excluded by emergency computed tomography (CT) or magnetic resonance imaging (MRI) (58). If available, MRI is very useful in the acute situation, either in excluding alternative pathologies or in confirming vascular disease.

Venous sinus thrombosis may be accompanied by haemorrhagic or bland infarction, typically parietal; MR venography usually demonstrates the occluded sinus. Electroencephalography (EEG) in cases of hemiplegic migraine usually shows unilateral slow background activity, but this may not distinguish clearly between stroke and migraine without MRI. Acute disseminated encephalomyelitis is usually obvious on MRI. Epilepsy with post-ictal hemiparesis may be assumed on EEG when epileptic activity can be found, but seizures may certainly also be caused by stroke.

Strategies for investigations and underlying conditions

In view of the great variety of conditions underlying paediatric ischaemic stroke, the spectrum of different investigations is individualised for each affected child. More detailed lists of essential and debatable types of investigation for underlying diseases and prothrombotic risk factors with respect to different ethnic backgrounds are discussed in the literature (9, 16, 37, 40, 58, 59).

Neuroimaging strategies

Based on the literature search, the strategy for neuroimaging is summarised in Table 2 (59-63). The identification of extra- and intracranial arterial diseases has been considerably improved by the use of magnetic resonance angiography (MRA). This non-invasive technique appears to be a sensitive and specific means of evaluating vasculopathies in childhood stroke (59, 62, 64, 65). The presence of vasculopathy may be suggested by transcranial Doppler sonography (TCD) and duplex ultrasound techniques, which are useful in screening. If arterial dissection is suspected, additional MRI of the neck with fat saturation or MRA of the cervical arteries is mandatory. However, conventional contrast angiography remains the reference examination for the diagnosis of arterial pathologies and should be considered in situations where MRA is normal, small arterial disease is suspected, or the possibility of dissection has not been excluded in MRA (15). In the acute phase, newer MR techniques such as diffusion and perfusion imaging may provide additional information (59, 66-68).

Vascular pathology and clinico-radiological patterns

Children with an infarct in an arterial territory should undergo vascular imaging (15, 64), which often shows large vessel disease. One of the main issues is the differentiation of primary vasculopathy and embolus from an extracerebral location, e.g. the placenta in neonates or a structurally abnormal heart. The most common abnormalities seen on MRA are stenosis or occlusion of the large cerebral arteries, although in rare cases the small vessels may be involved in a vasculitic process, which usually requires conventional arteriography for diagnosis.

Neuroimaging methods	Further imaging methods
Magnetic resonance imaging <ul style="list-style-type: none"> • With fat saturation: To detect dissection¹ • Diffusion- weighted² • Perfusion³ • Magnetic resonance angiography (MRA) (Circle of Willis and neck) 	Electroencephalogram
Transcranial and extracranial Doppler ultrasound	Transoesophageal echocardiography
Conventional cerebral angiography ⁴	Precordial echocardiography: bubble contrast
(Computed tomography): To exclude bleeding episodes	
(Gradient-echo imaging): To detect haemorrhage	
¹ T1-weighted spin echo with fat saturation sequence of the neck in addition to exclude dissection ² Diffusion imaging demonstrating areas of acute cytotoxic oedema ("core" of ischaemia) ³ Perfusion imaging to demonstrate areas of abnormal cerebral blood flow, blood volume and mean transit time ("tissue at risk") ⁴ Conventional angiography if MRI and MRA are normal and dissection or vasculitis must still be considered to be a differential diagnosis	

Table 2: Imaging methods and further diagnostic tools in children with ischaemic stroke.

Because of the increasing use of vascular imaging in childhood stroke, distinctive non-atherosclerotic arterial vasculopathies may be found: These stenosing vasculopathies can be divided into three distinct entities: transient (reversible), stable and progressive arteriopathies, which may be of prognostic relevance with respect to the risk of recurrence and to outcome (14, 69-71). However, as the natural history has not been well documented, the individual course of a stenosing vasculopathy may be difficult to categorise, especially at the time of initial presentation. Therefore, serial follow-up neuroimaging is essential in cases with arteriopathy to clarify the individual course, whereas the ideal methods as well as the time intervals need to be evaluated in further controlled studies. Because of the lack of evidence-based recommendations, non-invasive methods might be given preference in follow-up investigations aimed at distinguishing between the different courses of vasculopathies: If available, Doppler ultrasound techniques (every six months) and MR angiography (6 or 12 months after stroke onset) may be suggested, but angiography has also to be discussed in selected cases (15, 69, 70, 72).

The four main vasculopathies are elucidated below in greater detail: *Arterial dissection*: Dissection of the extracerebral vertebral and carotid arterial wall is an underestimated cause of stroke in childhood, accounting for up to 20% of cases (14, 16, 73). Classically, cervical injury is followed by neck pain and symptoms and signs of cerebral ischaemia but the associated trauma may be minimal. Stroke is usually secondary to

arterio-arterial embolism from the site of the initial intimal injury (60, 73-75).

Transient cerebral arteriopathy (TCA): Patients presenting with this condition share clinico-radiological features (70, 72). All were previously healthy children with acute hemiplegia as the initial neurological deficit. Cerebral imaging shows small subcortical infarcts located in the basal ganglia and internal capsule. Arteriography reveals multifocal lesions of the arterial wall, with stenosis or segmental narrowing in the distal internal carotid and the proximal anterior, middle or posterior cerebral arteries. Longitudinal arteriographic follow-up can show initial worsening of the arterial lesions for up to 7 months, followed by complete regression, improvement or stabilisation. The lack of late recurrence of strokes and the improvement or stabilisation of arterial lesions favour a transient physiopathological process, although longitudinal studies in large populations are required to define the natural history (76). The origin of TCA is unknown but may be an inflammatory response associated with prior viral infection such as Varicella (14, 70, 72, 77).

Fibromuscular dysplasia: Fibromuscular dysplasia (FMD) is a segmental, non-atheromatous, non-inflammatory angiopathy of unknown aetiology affecting medium- and small-sized arteries (78-80). The diagnosis of FMD is made by cerebral angiography (64, 78, 80): The most frequent pattern is multifocal short stenoses with mural dilatations, producing the typical string of beads appearance, and less commonly there is uni- or multifocal tubular stenosis.

Moyamoya syndrome: Moyamoya syndrome is commonly associated with stroke in Japan but is also seen in other paediatric populations in association with up to 20% of arterial brain infarcts (21, 43, 71). From a pathophysiological point of view, moyamoya syndrome appears to be a non-specific reaction to gradual occlusion of the distal carotid artery resulting from a variety of aetiologies, with multiple collaterals providing distal blood flow. Moyamoya *disease* has recently been found to be genetically linked to at least two loci, namely 17q25 and 3p24.2-p26. Neurofibromatosis type 1, sickle cell disease, Down syndrome, chronic inflammatory vasculitis, and exposure to radiation are also associated with moyamoya *syndrome*. Moyamoya in childhood is characterised by repeated ischaemic strokes, leading in many patients to severe neurological and cognitive disabilities, especially in those presenting before the age of 5. In some patients the underlying cause is treatable.

With respect to the different forms of vasculopathies, it has to be emphasised again that there may be an overlap in these defined subgroups (for example FMD as the basis for a dissection) (78). In addition, the possible relationship between vascular entities and concomitant triggers or underlying conditions, such as trauma and dissection, sickle cell disease and stenosing vasculopathies (68), TCA and infections (Varicella) has to be discussed: Although TCA might be found in several cases as post-Varicella vasculopathy, not all cases of TCA are associated with Varicella, and not all patients with stroke after chickenpox develop a stenosing vasculopathy or vice versa (7, 77, 81).

Cardiac disease

Cardiac disease is a common underlying disease in paediatric ischaemic stroke patients. The majority have congenital cyanotic or complex heart malformations or acquired heart diseases, like endocarditis or cardiomyopathy. Most of the affected children develop stroke in association with additional triggering risk factors such as cardiac procedures (surgery, biopsy, intervention) or non-cardiac events (immobilisation, other underlying diseases), often leading to activation of the coagulation system (9, 10, 16). For complex cardiovascular malformations which undergo the Fontan procedure, the risk of stroke seems to extend to several years after surgery, with the highest incidence in the first year after the operation (82). Relatively few children with stroke have previously unrecognised cardiac abnormalities, such as patent foramen ovale (PFO) with significant shunting (83, 84). In only a small proportion of the children with underlying cardiac malformation or disease can intracardiac thrombus formation be detected, and paradoxical embolism may be discussed as one mechanism for stroke.

However, the source is rarely found and some of these patients have evidence for venous sinus thrombosis or primary vasculopathy rather than embolism, so that neuroradiological imaging should always be performed as stated above with

respect to these diagnoses, in addition to cardiac and venous investigations.

Cardiac examinations should include transthoracic echocardiography (TTE) and electrocardiography (ECG) in all patients. In children with suspected PFO, bubble contrast may be given during precordial or transoesophageal echocardiography or TCD (16, 39, 84, 85).

According to the suspected pathomechanism with suggested paradoxical embolism due to venous-arterial shunting in underlying cardiac disorders, venous imaging should be performed in neonatal stroke as well as in suspected cardiac disorders. In the search for the source of emboli, central venous line thrombosis and renal vein thrombosis should be checked out. For cerebral venous evaluation, sonographic techniques (coloured duplex and compression techniques) as well as further radiographic imaging methods (CTMR venography) might be used in individual cases (34, 49, 53).

Conventional risk factors

Relatively little research has considered conventional risk factors for stroke in adults (10), as these have been assumed to be of little relevance to children. Although diabetes is rarely associated with vascular disease in childhood, the possibility of passive smoking playing a role cannot be discounted, and there appears to be an association between hypertension and vasculopathy (16). Chronic hypoxaemia is a risk factor for CNS events in sickle cell disease (86), and may play a role in other conditions e.g. cyanotic congenital heart disease (10). Additionally, careful clinical examination and control of routine investigations is important and can lead to the diagnosis in the single affected child. Such investigations include infection screening and examination of the cerebrospinal fluid in children with suspected parainfectious vasculitis (e.g. Varicella or mycoplasma) and full blood count with respect to polycythaemia and anaemia, which is also common, often secondary to iron deficiency (16). Some children have disorders of the lipid metabolism as well as metabolic diseases, as mentioned above (10, 36, 54).

Prothrombotic risk factors

Besides the underlying triggering factors mentioned above, acquired or inherited prothrombotic risk factors may play a role in the paediatric population with ischaemic cerebrovascular accidents (10, 16, 19-42). The distribution of prothrombotic risk factors reported here, however, may vary in different countries, depending on the ethnic population background (16, 30, 33, 37), the underlying disease and the number of patients/controls investigated (19, 33, 39, 40). Thus, to estimate the individual patient risk, it is recommended that symptomatic patient groups should be investigated in comparison with age- and gender-matched healthy controls from the same geographic catchment areas (87).

Based on the data obtained from case-control studies, at least the symptomatic propositus should be screened in a specialised coagulation unit for the prothrombotic defects listed in Table 3. Protein-based assays, i.e. APC resistance, protein C activity (first step) and antigen (second step), free and total protein S antigen, antithrombin activity (first step) and antigen (second step), lipoprotein (a) and fasting homocysteine concentrations should be investigated 3 to 6 months after the acute stroke onset along with DNA-based assays, i.e. factor V G1691A mutation, prothrombin G20210A variant and MTHFR C677T genotype. However, potential variations are unavoidable due to differing ethnic population backgrounds. In addition, rare prothrombotic defects, e.g. dysfibrinogenaemia, hypo-/or dysplasminogenaemia, heparin cofactor II deficiency, factor XII deficiency, increased levels of histidine-rich glycoprotein, protein Z or further genetic polymorphisms, should be kept in mind. Besides being tested for prothrombotic defects as stated above, all symptomatic children with thromboembolic stroke should be screened for the presence of increased IgM or IgG antiphospholipid/anticardiolipin or anti- β 2-glycoprotein I antibodies and the presence of lupus anticoagulants (8, 25, 32).

Outcome and recurrence

Although mortality is much lower than in adults and appears to be declining (88), outcome is poor in up to 60% of children (89, 90). A residual motor deficit is common and there may also be additional subtle cognitive deficits and behavioural difficulties, which may have a significant impact on employment prospects and family functioning (47, 51, 52, 54, 89, 91, 92).

The overall risk of recurrent stroke ranges from less than 10% up to 30% (14, 40, 46, 70, 93, 94). Preliminary data suggest that stroke recurrence is associated with the presence and severity of the vasculopathy (14, 46) as well as with prothrombotic risk factors (inherited protein C deficiency and familial

elevated lipoprotein (a) levels) (40). Most, but not all, of these recurrences occur within 6 months of the initial stroke, but some patients, especially those with sickle cell disease, have a significant long-term risk (93). Recurrent stroke usually causes a significant increase in disability, and it is therefore important to look carefully for risk factors in order to attempt secondary prevention.

Treatment of childhood stroke

In contrast to adulthood, there are no randomised clinical trials in childhood, so that established guidelines for primary prevention, short-term treatment and secondary prevention of paediatric ischaemic stroke are still lacking. Treatment strategies are partially based on case series and reports, but are mainly extrapolated from studies in adult patients. With respect to the differences in underlying conditions for paediatric ischaemic stroke, all these treatment strategies remain optional and must be debated in each individual child. For interested readers, more detailed information on this controversial field can be found in the literature (58, 95).

In adults, the main focus of recent studies has been the search for acute treatment to minimise the effect of the initial stroke, using either thrombolysis or neuroprotection (96, 97). Treatment by thrombolysis within the first hours after stroke onset seems to have an advantage - the risk of haemorrhage in adults is less than 10%. However, thrombolysis increases the risk of intracranial haemorrhage significantly. Nevertheless, most studies show an improvement in outcome with respect to death and dependency (98, 99).

Although children with stroke often present to a doctor within 3 hours, the diagnosis is rarely made with any degree of certainty at this stage because of the rarity of stroke, the low sensitivity of CT for acute infarction and the wide differential

Plasma/protein-based*	DNA-based
APC-R (APC resistance)	Factor V G1691A
Protein C activity/ antigen	Prothrombin G20210A
Free and total protein S antigen	MTHFR C677T
Antithrombin activity/antigen	
Lipoprotein (a)	Further potential polymorphisms
Fasting homocysteine	
Lupus anticoagulant / antiphospholipid antibodies	
Fibrinogen (Clauss)	
Plasminogen	
Factor VIII C	
Factor XII	

* three to six months after the acute stroke onset

Table 3: Screening in symptomatic paediatric patients suffering from ischaemic stroke (may be modified with respect to different ethnic population backgrounds).

diagnosis in this age group (100). In addition, mortality is lower and most children presenting with stroke can expect to lead independent lives as adults. Due to the lack of controlled studies in this field, only case reports of thrombolysis in stroke children have been published: These case reports concluded that the use of thrombolytic agents in stroke following cardiac surgery or in children suffering from basilar thrombotic occlusion resulted in recanalisation and good clinical recovery in the majority of cases (101-104). Disastrous results of thrombolysis following stroke in children have not been reported to date in the literature, but an elevated risk of haemorrhage is also discussed in this age group (58, 105). Interestingly, the time interval between stroke event and thrombolysis in single cases is more than 3 or 6 hours in children (102, 103). In summary, there remains a lack of thrombolysis studies in children with stroke, and the risk/benefit ratio of thrombolysis is therefore not clarified. Thus, it is difficult to see a major role for t-PA in this age group at the present time, although it may occasionally be justified in children when diagnosis is confirmed within an early time window and persistent arterial occlusion with hypoperfusion may lead to a further increase of the infarcted area (102).

Infarct volume and outcome appear to be related to body temperature during the first few days of the stroke; a direct causative effect remains unproven, but maintaining body temperature just below 37°C is unlikely to do harm. Apart from preventing fever, there is no neuroprotective strategy available at the present time which could be recommended for use in children.

There are, nevertheless, a number of management strategies for individual patient groups which may make a difference. Seizures in the acute phase should be managed appropriately, and there is a case for surgical decompression in children presenting in coma with large ischaemic middle cerebral infarcts (106), which are almost always fatal if managed conservatively. In children with sickle cell disease, exchange transfusion is recommended as an acute measure, although this must be conducted slowly and with caution, in view of the association with neurological deterioration (12).

In patients with moyamoya syndrome or disease, revascularisation surgery using different techniques like myoangiostomy [direct application of superficial temporal artery on the surface of the brain with or without a fragment of muscle (107)], direct extracranial-intracranial bypass (108) or a combination of both methods (107) may be helpful (109, 110). The goal is to obtain an increase in cerebral blood flow to the ischaemic tissue, either directly by bypassing the blockage in the supplying artery or indirectly by inducing sprouting of tiny arterial branches penetrating the brain. However, there is no evidence-based confirmation of the efficiency of surgical treatment, perhaps because there are wide differences in technique between centres. Retrospective studies have shown no difference between surgical and non-surgical treatment in terms of

outcome (111), while other studies offer some evidence that revascularisation surgery may lead to a beneficial outcome regarding recurrence risk and TIAs. Up to now, however, the quantity of data available is limited, so that the best time for surgery as well as the extent of revascularization are controversial and prospective comparative studies (surgery versus medical treatment alone) and clear recommendations are still missing (110, 112-115). Thus, treatment with antiplatelet agents remains a first step, as prothrombotic disorders are commonly associated, but follow-up must be tight (71) as there is commonly cognitive deterioration (116).

The acute management of the remaining patients remains controversial. Despite the risk of haemorrhage, there are patient groups, e.g. those with vessel dissection and known prothrombotic abnormalities, who should probably be anticoagulated acutely to prevent early recurrence. As arterial dissection entails the risk of recurrent arterio-arterial embolism, anticoagulation has been the most widely used treatment: According to recently published guidelines, heparin given initially with conversion to warfarin or antiplatelet agents after 3- to 6-months is indicated in arterial dissection (74, 117). With respect to recent studies, low molecular weight heparin (LMWH) might be preferred in children as a safe drug and an efficacious alternative to the use of unfractionated heparin (118-122).

Nevertheless, the evidence for benefit of anticoagulation, bearing in mind the risk of haemorrhage, remains weak. For adult patients, besides thrombolysis the use of aspirin is recommended as soon as possible (within 48 hours): Aspirin was reported to be associated with a modest improvement in outcome and a decrease in recurrence risk and death in two very large controlled trials in adults, probably because of a reduction in early recurrence and perhaps, in addition, through its antipyretic effect (96). The risk of haemorrhage appears to be lower than with anticoagulants, and although there has been no controlled trial in children, aspirin should probably be given acutely unless there are contraindications.

With respect to antithrombotic drug treatment, although there is as yet no evidence that the use of antiplatelet agents or anticoagulation is beneficial in childhood, the use of antithrombotic drugs in children should also be discussed. As with the administration of antithrombotic drugs for acute stroke treatment in children, secondary prevention aimed at reducing the risk of recurrence is a controversial field in childhood stroke. In a prospective but non-randomised study in a cohort of 135 consecutively recruited stroke children aged ≥ 6 months to ≤ 18 years, no significant difference was found between the use of aspirin and low-dose low molecular weight heparin administered after a first symptomatic ischaemic stroke with respect to restroke and drug-related side effects (123). Today, the decision on whether and how to treat is still the individual decision of the physician responsible for the child, and many physicians decide not to use any specific antithrombotic treatment. The reported

frequency with which antiplatelet or anticoagulant agents are used in stroke children seems to be less than 50%. No study demonstrating any advantage of one of the treatment options mentioned has been published to date. However, since no data on severe adverse effects of the diverse antithrombotic/anticoagulant drugs and applications discussed for use in stroke children are available, treatment options which may be used include the administration of LMWH, aspirin or warfarin. Long-term antithrombotic treatment and its corresponding risk/benefit profile remain open, and this issue has to be clarified in large-scale international controlled trials (122, 123). New data, case series and prospective follow-up studies characterising potential candidates for stroke recurrence have been recently published (31, 40, 94, 124). The latter might influence the practice of individual treatment decisions, pointing out the need for future large-scale international trials.

Strategies for further stroke studies in children

International collaboration will be essential in estimating the distribution and impact of stroke in children. Research must be conducted in well-defined populations, using the same clinical instruments and with clearly defined follow-up. Similar imaging methods, laboratory investigations and treatment modalities must be used and objective study endpoints should be prospectively defined. In order to avoid classification errors which may

lead to spurious conclusions, it is very important to compare children with stroke from different countries or ethnic backgrounds with respect to underlying diseases, acquired and genetic. In addition, the measurement methods applied to both cases and controls should have adequate sensitivity and specificity in predicting outcomes. On the one hand, a useful tool may be case-control studies with cases and controls from the same catchment areas to minimise selection bias. On the other hand, when control children are not available for ethical reasons, a second option for obtaining sufficient data, for example on the rate of restroke with respect to the presence of vascular disease or inherited prothrombotic risk factors, is data pooling. For randomised studies of treatment, however, clear a priori definitions will be important with respect to stroke subgroups (cryptogenic or symptomatic secondary to cardiac pathology or sickle cell disease), triggers (prothrombotic disorders, trauma, infection, hypoxia, migraine) and likely mechanisms (embolus, vasculopathy: transient, stable or progressive). Thus detailed acute investigation will be essential so that groups can be compared across the participating study centres. Careful planning and consideration of the problems likely to be encountered during the data collection phase are recommended for future collaborative studies in paediatric stroke.

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