Prospective assessment of risk factors for recurrent stroke during childhood—a 5-year follow-up study

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Summary

Background Risk factors for arterial stroke in children include congenital heart malformations, vasculopathies, infectious diseases, collagen tissue diseases, and metabolic disorders. Results of previous case-control studies have shown an association between ischaemic stroke and hereditary prothrombotic risk factors: factor V G1691A and factor II G20210A mutations, raised lipoprotein (a), and deficiencies in antithrombin, protein C, and protein S. The relevance of these factors to a second ischaemic stroke event is not known.

Methods We assessed the risk of a second arterial ischaemic stroke associated with these prothrombotic risk factors, with underlying diseases or stroke comorbidities, and with stroke subtypes (cardiac, vascular, infectious, idiopathic). 167 boys and 134 girls aged between 6 months and 18 years of age (median 7 years) with a first episode of ischaemic stroke were followed-up prospectively for a median of 44 months (range 20–56).

Findings Recurrent ischaemic stroke was diagnosed in 20 of 301 children who survived (6·6%) at a median of 5 months (range 1·5–36) after first stroke onset. The relative risk of having a second stroke was significantly increased in patients with raised lipoprotein (a) (relative risk 4·4, 95% CI 1·9–10·5) and in children with familial protein C deficiency (3·5, 1·1–10·9). Additionally, survival analysis showed that a first ischaemic stroke of vascular origin was significantly associated with having a second stroke (odds ratio 3·9, 95% CI 1·4–10·6).

Interpretation Raised lipoprotein (a), protein C deficiency, and stroke of vascular origin are risk factors for recurrent arterial ischaemic stroke in childhood.

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*The Childhood Stroke Study Group

Introduction

The incidence of stroke in children is estimated at about 2·6 per 100 000 per year,[1] with half of reported events presenting as arterial ischaemic strokes. Risk factors for cerebrovascular accidents in children include congenital heart malformations, vasculopathies, infectious diseases, and collagen tissue diseases, as well as some rare inborn metabolic disorders.[1–3] Additionally, the presence of prothrombotic risk factors—factor V G1691A and factor II G20210A mutations, raised concentrations of lipoprotein (a) and homocysteine, as well as deficiency of the natural anticoagulants antithrombin, protein C, and protein S—have been found in small case series and case-control studies to be associated with ischaemic stroke in infants and children.[4–11] Few data are available from prospective studies about the role of hereditary risk factors, especially their prognostic potential for a second stroke event in paediatric patients. In small case series the short-term rate of a second stroke is about 20%, ranging from 8% in children with no identified underlying disorder to 42% in those with several risk factors.[12,13] We therefore investigated, in a prospective study, the relevance of underlying stroke subtypes,[14] organic and metabolic diseases, and prothrombotic risk factors to a second stroke in children.

Methods

Study population and design

From October, 1995, to October, 2000, we consecutively recruited 324 white infants and children aged between 6 months and 18 years (median age at onset of first arterial stroke 7 years, range 7 months to 18 years; 179 boys and 145 girls) from various geographic areas of Germany. This group size is equivalent to 1·1 per 100 000 of the paediatric population aged older than 6 months in Germany. 65% came from northern, western, and eastern Germany—ie, the catchment areas of Hamburg, Kiel, and Lübeck (10%); Münster (15%); Bielefeld (5%); Düsseldorf (7%); Berlin, Magdeburg, and Halle (10%); and Frankfurt/Main (18%)—and 35% from southern Germany (overall catchment area of Munich). In these children the first arterial ischaemic stroke was confirmed by CT, MRI, magnetic resonance angiography, and conventional angiography.[7] Patients with onset of a first symptomatic stroke were recruited consecutively without establishment of whether or not prothrombotic risk factors were present. Neonates and infants younger than 6 months of age, and children with sickle-cell disease (n=2) were not included in this investigation.

Classification of stroke subtypes at first stroke onset was done in part with reference to Mathews[15] and to Kirkham and colleagues,[2] in association with underlying diseases or comorbidities and medical history, results of MRI methods including magnetic resonance angiography, conventional angiography, and doppler ultrasonography; transthoracic and transoesophageal echocardiography with saline contrast; and electrocardiography. We classified patients into four subgroups: cardiac stroke, vascular stroke, stroke directly associated with infectious diseases, and idiopathic stroke (panel). Additionally, two

children with associated infectious diseases and a persistent vasculopathy during the follow-up were classified into the vascular subgroup.

The study endpoint was defined as recurrent ischaemic stroke confirmed by MRI, magnetic resonance angiography, or conventional angiography. Transient ischaemic attacks did not qualify as second stroke events. In all patients recruited with a first symptomatic stroke, adequate imaging methods were routinely repeated after 4–6 weeks, 3–6 months, 12 months, and then yearly. In patients with a possible second arterial stroke, images were obtained within 24 h of hospital admission with a control image before hospital discharge. The clinical diagnosis of a recurrent ischaemic stroke was additionally confirmed by an independent neuroradiologist.[7]

At the discretion of the study centres, paediatric patients with a first stroke onset received vitamin K antagonists (n=4), antiplatelet agents (n=52), or low-dose low-molecular-weight heparin (n=89). In the remaining 156 patients no secondary antithrombotic therapy was given.[16]

Basic classification of stroke subtypes used (not including haematological or coagulation disorders[2,17,18]

Cardiac
Congenital heart disease
Infective endocarditis
Valvular disease
Arrhythmia
Patent foramen ovale

Vascular
Arterial occlusive disease
  Moyamoya
Primary vasculopathy
  Fibromuscular dysplasia
  Stenosis
  Vasculitis
Secondary vasculopathy
  Dissection
  Trauma (catheter, surgical intervention)
  Intraoral trauma

Infectious
Acute infections of the CNS
  Meningitis
  Encephalitis
Infections outside the CNS
  Head and neck infection
  Sepsis
  Varicella
  AIDS
  Haemolytic-uraemic syndrome

Neurocutaneous syndromes
Neurofibromatosis
Tuberous sclerosis
Sturge Weber

Metabolic
Homocystinuria
Lactic acidosis and stroke-like episodes (MELAS)

Drugs
Cocaine
Sympathomimetics
Oral contraceptives
Escherichia coli asparaginase

Idiopathic

This prospective multicentre follow-up study was done in accordance with the ethical standards stated in the updated version of the 1964 Declaration of Helsinki, and was approved by the medical ethics committee of the University of Münster.

Laboratory tests

With written or oral parental consent, we investigated the factor V G1691A and factor II G20210A mutations, resistance to activated protein C, and concentration of lipoprotein (a), protein C, protein S, antithrombin, and antiphospholipid antibodies, with standard laboratory techniques at stroke onset and 3–6 months after the acute stroke event.[7,17] A type I deficiency (antithrombin, protein C) state was diagnosed when functional plasma activity and immunological antigen concentrations of a protein (tested every 3–6 months) were repeatedly shown to be below 50% of the normal age-related limit.[18] A type II deficiency (antithrombin, protein C) was diagnosed in patients with repeatedly low functional activity along with normal antigen concentrations. The diagnosis of protein S deficiency was based on reduced concentrations of free protein S antigen combined with decreased or normal total protein S antigen concentrations. Serum concentrations of lipoprotein (a) higher than 300 mg/L were regarded as raised, and 28 kringle IV was used as the cutoff for the definition of small apolipoprotein A isoforms (subgroup analysis n=77).[7] Criteria for the hereditary nature of a haemostatic defect were its presence in at least one first or second degree family member, or the identification of a causative gene mutation, or both.

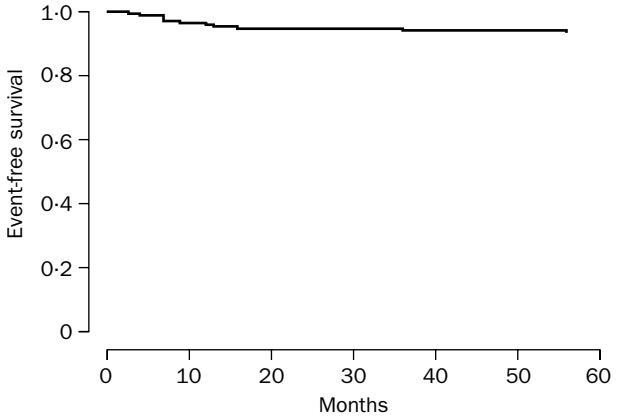
Statistical analysis

All statistical analyses were done with the StatView 5 software package (SAS Institute). The estimated relative risk (RR) and 95% CI were calculated to compare the rate of restroke in carriers of prothrombotic risk factors with that of patients without an identified genetic risk. The probability of recurrent ischaemic stroke as a function of time was determined with the method of Kaplan and Meier. To evaluate an independent contribution to the risk of recurrent ischaemic stroke and to adjust for potential confounders, prothrombotic risk factors, the mode of antithrombotic treatment used, and the different stroke subtypes, the hazard ratio together with 95% CI were estimated from Cox's proportional hazards model. To further describe the relation between independent and dependent variables, we did the likelihood ratio test. Because of their seemingly non-Gaussian distribution, continuous data were presented as medians and ranges and assessed by non-parametric statistics with the Wilcoxon-Mann-Whitney *U* test. To compare frequency distributions of fatal outcome, Fisher's exact test was used, and we calculated exact 95% CIs. p values lower than 0·05 were regarded as significant.

	Number of patients (%)
Underlying basic diseases	123/324 (38%)
Previous vascular event	0/324
Positive family history	125/324 (39%)
Antithrombotic treatment	145/301 (45%)
Male	167/301 (55%)
Prothrombotic risk factors*	
APC resistance	1·7 (1·2–1·9)
Lipoprotein (a) (mg/L)	170 (<30–1800)
Protein C activity (U/mL)	0·85 (0·08–1·22)
Free protein S antigen (U/mL)	0·75 (0·06–1·30)
Antithrombin (U/mL)	0·95 (0·20–1·32)

*Beyond the acute stroke onset. Data for prothrombotic risk factors are median values (range).

Table 1: **Clinical characteristics of study population**



Overall event-free survival in paediatric patients with a first ischaemic stroke

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

324 patients with onset of first stroke were identified. Five patients died during the first stroke onset, 12 were excluded due to loss of follow-up, and in six cases parents did not give their consent to participation in the study: thus, the final study population (table 1) comprised 301 children, who were followed up for a mean of 44 months (range 20–56). The brain lesions at first stroke onset were found predominantly in the territories of the left middle cerebral artery (n=153), right middle cerebral artery (n=76), or vertebrobasilar system (n=38); bilateral cerebral infarction was diagnosed in 34 patients. Within a median follow-up time of 5 months (range 1·5–36) 20 of the 301 children (6·6%) had a second stroke event, and three of these 20 patients died immediately (15%, one of cardiac stroke and two of idiopathic stroke). Compared with the fatal outcome associated with the first stroke—ie, five of 306 children (1·6%)—this death rate was significantly increased (p=0·0017). In most cases (15 of 20), the same vascular territory was implicated as in the first stroke. The brain lesions at second stroke onset were found in the territories of the left middle cerebral artery (n=5), right middle cerebral artery (n=6), bilateral infarction (n=3), or within the vertebrobasilar system (n=1). The remaining five children presented with recurrent ischaemic stroke in the territory of the contralateral middle cerebral artery (n=4), and with bilateral infarction (n=1). The figure shows the overall event-free restroke survival in children who had a first ischaemic stroke.

	Number at onset	Cases of second stroke (%)
Subtype		
Cardiac	37 (12·3%)	1 (2·7%)
Vascular stroke (overall rate)	54 (17·9%)	8 (14·8%)
Dissection or trauma	21 (38·9%)	1 (4·8%)
Fibromuscular dysplasia	9 (16·7%)	1 (11·1%)
Moyamoya	7 (13·0%)	2 (28·6%)
Stenosis	12 (22·2%)	3 (25·0%)
Vasculitis	5 (9·3%)	1 (20·0%)
Infectious	29 (9·6%)	1 (3·4%)
Idiopathic	181 (60·1%)	10 (5·5%)
Total	301 (100%)	20 (6·6%)

Table 2: **Prevalence of first stroke subtype and of second stroke subtype in relation to first stroke subtype (descriptive analysis)**

	Number at onset	Cases of second stroke*
Risk factor		
Protein C deficiency	16 (5·3%)	3 (18·8%, 4·0–45·6)
Protein S deficiency	12 (4·0%)	2 (16·7%, 2·0–48·4)
Lipoprotein (a) >300 mg/L	61 (20·3%)	10 (16·4%, 8·1–28·0)
Factor II G20210A	12 (4·0%)	1 (8·3%, 0·2–38·4)
Factor V G1691A	43 (14·3%)	1 (2·3%, 0·1–12·2)
Antithrombin deficiency	3 (1·0%)	–
Antiphospholipid antibodies	22 (7·3%)	–
None	132 (43·9%)	3 (2·3%, 0·4–6·5)
Total	301 (100%)	20 (6·6%, 4·1–10·1)

*Data are number (%, 95% CI)

Table 3: **Prevalence of prothrombotic defects in paediatric ischaemic stroke in first stroke, and in second stroke in relation to first (descriptive analysis)**

Table 2 shows the number of second strokes by stroke subtype: a second stroke of vascular origin (p=0·01) happened more frequently than a second stroke in the other stroke groups. With respect to classifications mentioned in the methods section, stroke of vascular origin was defined as stenosing vascular disorders diagnosed with non-invasive tools (sonography, MRI, and magnetic resonance angiography) in all patients, and with digital subtraction angiography in selected cases. Stenosing vasculopathies were caused by trauma or dissections of the cerebral arteries, fixed or progressive stenoses of the vessels—eg fibromuscular dysplasia, circumscribed non-specific stenosis, or moyamoya syndrome—and vasculitis. One of four children who had a first stroke after chickenpox showed fixed stenoses of the middle and posterior cerebral arteries.[19] Additionally, a 3-year-old boy had long-standing stenosis of the right middle cerebral artery after herpes simplex type I infection. However, only one child with associated infectious disease and without persistent stenosing vasculopathy has had a second stroke event so far.

Patients with familial protein C deficiency showed the highest rate of restroke, followed by children with protein S deficiency, patients with raised lipoprotein (a), and carriers of factor II and factor IV mutations (table 3). In our patients resistance to APC was clearly associated with the common factor V G1691A mutation in all children. No patients with stroke had acquired APC resistance, and whether resistance to APC is additionally combined with the factor V HR2 haplotype is under investigation (unpublished data).

	Odds ratio (95% CI)	p*
Prothrombotic risk factor		
No prothrombotic risk	1 (reference)	
Lipoprotein (a) > 300 mg/L	2·8 (1·1–7·5)	0·04
Protein C deficiency	10·7 (2·5–45·8)	0·005
Protein S deficiency	0·6 (0·05–6·4)	0·63
FV G1691A	0·3 (0·4–2·3)	0·17
FII G20210A	1·8 (0·2–15·0)	0·60
Antithrombotic treatment		
None (reference)	1·0	
Antiplatelet agents, heparin, or vitamin K antagonists	1·8 (0·6–5·3)	0·24
Stroke subtypes		
Idiopathic stroke (reference)	1·0	0·04
Vascular stroke	3·9 (1·4–10·6)	0·007†
Cardiac stroke	0·3 (0·03–3·4)	0·36†
Infectious stroke	1·4 (0·2–11·3)	0·76†

*Likelihood ratio p value, except †Wald p value.

Table 4: **Independent contributions to the risk of a second ischaemic stroke for prothrombotic risk factors, antithrombotic treatment, and stroke subtypes**

	Idiopathic stroke	Cardiac stroke	Vascular stroke	Infectious stroke
Drugs used				
None	3/95 (3%, 0·6–9·0)	0/22 (0%, 0–15·4)	2/21(10%, 1·1–30·4)	0/18 (0%, 0–18·5)
Aspirin	1/22 (5%, 0·1–22·8)	0/5 (0%, 0–52·2)	3/18 (17%, 3·5–41·4)	1/5 (20%, 0·5–71·6)
Low-molecular-weight heparin	6/61(10%, 3·7–20·2)	1/10 (10%, 0·2–44·4)	2/12 (17%, 2·0–48·4)	0/6 (0%, 0–45·9)
Vitamin K antagonists	0/1*	..	1/3† (33%, 0·8–90·6)	..
Clopidogrel	0/2	..	..	..
Total	10/181 (6%, 2·7–9·9)	1/37 (3%, 0·0–14·2)	8/54 (15%, 6·6–27·1)	1/29 (3%, 0·1–17·8)

International normalised ratio: *2·0–3·0, †2·1. Data are number of patients on specified drug with specified stroke type/total number of patients on specified drug (%,95% CI).

Table 5: **Stroke types and restroke rate by antithrombotic treatment (descriptive analysis)**

The estimated RR and 95% CI of a second stroke event associated with prothrombotic risk factors, however, was significantly increased only for patients with raised lipoprotein (a) (RR 4·4, 95% CI 1·9–10·5) and for children with confirmed protein C deficiency (3·5, 1·14–10·9). Additionally, subgroup analysis of patients with lipoprotein (a) phenotyping showed that patients with kringle 4 repeats of fewer than 28 also had an increased risk of a second stroke (4·4, 1·1–17·5). By contrast, the risk was not significantly increased in carriers of the factor V G1691A mutation (0·4, 0·05–2·8), the factor II G20210A genotype (1·3, 0·2–9·6), or protein S deficiency (2·9, 0·8–11·3). No second stroke was recorded in patients with antithrombin deficiency or antiphospholipid antibodies.

The Cox's proportional hazards model was used to establish the independent contribution to the onset of a second stroke of inherited prothrombotic risk factors, of antithrombotic therapy (table 4), and of stroke subtype. Of the prothrombotic risk factors we investigated, only the presence of increased lipoprotein (a) and protein C type I deficiency had significant and independent associations with the time to second arterial ischaemic stroke event. Additionally, vascular origin of first ischaemic stroke contributed significantly to the onset of a second stroke. The remaining stroke types and the mode of antithrombotic treatment did not significantly influence the risk of a second stroke in these patients (table 5).

Discussion

Our survival analyses provide evidence that increased lipoprotein (a) and protein C type I deficiency are independent risk factors for recurrent ischaemic stroke in white paediatric patients. By contrast with previously published data and with first stroke onset in the patients investigated,[4–11] and by contrast with recurrent venous thromboembolism in children of a similar population, the factor V G1691A and factor II G20210A mutations, protein S, and antithrombin deficiency were not significantly associated with ischaemic restroke in our patients. However, since the prevalence of antithrombin and protein S deficiency is low in the German population, a larger group of patients than that analysed here should be investigated to ascertain whether protein S deficiency or further prothrombotic risk factors are also significant risk factors for a second stroke in children. The multivariate statistical model also showed that a first stroke based on cerebral vascular abnormalities increased the risk of restroke in this cohort. Since some of the cases were treated with antiplatelet agents, heparin, or vitamin K antagonists,[16] possibly confounding the outcome of the entire study group, the influence of this treatment on the rate of stroke recurrence was also investigated in the survival analysis. The treatments did not significantly influence the restroke rate.

Protein C deficiency was diagnosed 3–6 months after the first stroke onset. Heredity was confirmed by family studies. 5·3% of initial stroke patients and 18·8% of restroke patients had protein C deficiency in the cohort we investigated. On the one hand, this is within the rate of venous thrombosis. On the other hand, however, protein C deficiency has been described in children with stroke,[7–11] and sporadically in young adult stroke patients. Thus, since in our investigation transient acquired protein C deficiency[20] was ruled out by repeated measurements beyond the acute stroke episode, and since the defect was additionally identified in at least one family member for all patients, inherited protein C deficiency is clearly not only a coexistent pathogenic occurrence, but also an independent risk factor for ischaemic stroke and restroke in children.

The role of raised lipoprotein (a) as a risk factor for stroke has been controversially discussed since a number of case-control studies as well as one prospective study on this issue failed to find any association between increased lipoprotein (a) and stroke in the elderly.[21,22] However, several workers who did case-control studies with young adults or children found significant associations between stroke and raised concentrations of lipoprotein (a).[7,21] Thus, the cause of stroke and the coincidence of additional risk factors seem to affect the role of lipoprotein (a) as a risk factor for stroke. Obviously this cause or these concomitant risk factors are found in children with ischaemic stroke. Since protein C deficiency is also a risk factor for a second stroke, and since raised lipoprotein (a) has also been identified as a risk factor for venous thromboembolism in children and adults, procoagulatory or antifibrinolytic mechanisms, or both, should be regarded as important for arterial and venous thrombosis caused by raised lipoprotein (a). In accord with its close structural homology, lipoprotein (a) inhibits the activation of plasminogen by streptokinase and tissue plasminogen activator and competes with plasminogen for binding to fibrin as well as for binding to annexin II, the plasminogen/tissue plasminogen activator receptor on endothelial cells and platelets.[23,24]

Our data also show an increased risk of recurrent stroke events in the subgroup of patients with underlying vasculopathies. This observation has to be discussed in the context of patients with moyamoya syndrome, who have a naturally high tendency to recurrent stroke events.[2,13,25,26] In our series, moyamoya syndrome was diagnosed in seven of 54 children (13·0%) with vascular disorders, and in two cases it was responsible for second stroke events. The lower rate of stroke recurrence in these patients with moyamoya, however, is mainly due to the fact that four out of seven children underwent early revascularising surgical interventions, and that transient ischaemic attacks were not included as second strokes in our study. Additionally, a boy who did not have recurrent stroke developed moyamoya after brain tumour irradiation. Dobson and co-workers investigated moyamoya syndrome in childhood sickle-cell disease. In their cohort, 41% of patients with sickle-cell disease had a second stroke or transient ischaemic attack despite long-term transfusions, and the rate was even higher in patients

with moyamoya collaterals (11 of 19).[27] However, since other stenosing vascular disorders[2,28–30] are thought to lead to recurrent strokes events, large-scale studies are necessary to clarify whether stenosing vasculopathies other than moyamoya syndrome predispose to recurrence of stroke. Additionally, since we had excluded the two children with sickle-cell-associated stroke at the onset of the study, no conclusions can be drawn for this group of especially stroke-prone children from our data.

Few data relating to a second ischaemic stroke event in paediatric patients are available,[2,3,12,13] mainly because stroke is a rare vascular disorder at this age and the various underlying diseases differ from those of adult stroke populations. Furthermore, children with stroke have not been extensively investigated, on the assumption that outcome is generally associated with a good prognosis, low risk of recurrence, and good recovery of motor function and ability at school.[2] The restroke rate reported by us—ie, 6·6% of the patients enrolled, not including transient ischaemic attacks—is lower than the rate of about 20% reported by other investigators in small groups of paediatric stroke patients.[12,13] The difference observed is, however, due to different ethnic backgrounds, different patient populations, different numbers of children enrolled, and variations in underlying diseases.[13] Although the rate of second stroke events in our cohort is low compared with previous reports, our results give valuable information about paediatric patients at risk. Besides the recurrence rate of 6·6%, the overall death rate from recurrent stroke was 15%, a serious outcome which requires further discussion on its prevention in paediatric patients with stroke. Follow-up in this investigation was between 20 and 56 months; a follow-up of more than 5 years might identify higher restroke rates in the stroke subgroups investigated.

In summary, our data show that recurrent ischaemic stroke in childhood is a rare but serious event which arises soon after the first event and has a high fatality rate. Therefore, identification of children at increased risk because of raised lipoprotein (a), protein C deficiency, or stroke of vascular cause will help to improve preventive measures.

Contributors

All the authors took an equal part in the design and implementation of the study, in data analysis, and in writing the report.

Conflict of interest statement

None declared

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