Incidence and Outcomes of Symptomatic Neonatal Arterial Ischemic Stroke

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abstract

BACKGROUND AND OBJECTIVES: Neonatal arterial ischemic stroke (NAIS) is associated with considerable lifetime burdens such as cerebral palsy, epilepsy, and cognitive impairment. Prospective epidemiologic studies that include outcome assessments are scarce. This study aimed to provide information on the epidemiology, clinical manifestations, infarct characteristics, associated clinical variables, treatment strategies, and outcomes of NAIS in a prospective, population-based cohort of Swiss children.

METHODS: This prospective study evaluated the epidemiology, clinical manifestations, vascular territories, associated clinical variables, and treatment of all full-term neonates diagnosed with NAIS and born in Switzerland between 2000 and 2010. Follow-up was performed 2 years (mean 23.3 months, SD 4.3 months) after birth.

RESULTS: One hundred neonates (67 boys) had a diagnosis of NAIS. The NAIS incidence in Switzerland during this time was 13 (95% confidence interval [CI], 11–17) per 100 000 live births. Seizures were the most common symptom (95%). Eighty-one percent had unilateral (80% left-sided) and 19% had bilateral lesions. Risk factors included maternal risk conditions (32%), birth complications (68%), and neonatal comorbidities (54%). Antithrombotic and antiplatelet therapy use was low (17%). No serious side effects were reported. Two years after birth, 39% were diagnosed with cerebral palsy and 31% had delayed mental performance.

CONCLUSIONS: NAIS in Switzerland shows a similar incidence as other population-based studies. About one-third of patients developed cerebral palsy or showed delayed mental performance 2 years after birth, and children with normal mental performance may still develop deficits later in life.

WHAT'S KNOWN ON THIS SUBJECT: Neonatal arterial ischemic stroke is associated with later cerebral palsy and cognitive impairment. Many studies on neonatal ischemic stroke are limited by modest sample sizes, and prospective studies that include outcomes assessments are scarce.

WHAT THIS STUDY ADDS: Results from this prospective, nationwide, population-based study provide information on the epidemiology, associated clinical variables, clinical manifestation, vascular distribution, and treatment of neonatal arterial ischemic stroke. The study also provides outcomes regarding motor function and cognition.

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Various events during the perinatal period can lead to a focal interruption of the blood supply, leading to an ischemic stroke. When it occurs during the perinatal period, arterial ischemic stroke is associated with considerable lifetime burden such as cerebral palsy (CP), cognitive impairment, and epilepsy.[1–7] Various terms have been used to describe arterial ischemic stroke during the perinatal period. Because of a lack of consistency among studies, its terms were defined in a workshop of the National Institute of Child Health and Human Development and the National Institute of Neurologic Disorders and Stroke.[8,9] *Ischemic perinatal stroke* was defined as a focal disruption of cerebral blood flow occurring between 20 weeks of gestation and postnatal day 28. Because the exact timing of the stroke usually is unclear, ischemic perinatal stroke is defined according to gestational age or postnatal age at diagnosis. Three subcategories were defined. *Fetal ischemic stroke* is diagnosed before birth by use of fetal imaging methods or, in stillbirths, on the basis of neuropathologic examination. *Neonatal arterial ischemic stroke* (NAIS) is diagnosed after birth and on or before postnatal day 28 (including in preterm infants). *Presumed perinatal ischemic stroke (PPIS)* is diagnosed in infants >28 days of age in whom it is presumed (but not certain) that the ischemic event occurred sometime from week 20 of gestation through postnatal day 28.[8,9] Perinatal arterial ischemic stroke is not a rare condition. Hospital- and population-based studies in North America and Europe have provided epidemiologic data suggesting that the incidence of ischemic perinatal stroke is between 5 and 43 per 100 000 live births.[2,10–18] Studies have shown that about half of patients become symptomatic during the neonatal period.[14] A summary of epidemiologic studies on NAIS and PPIS is presented in Table 1.

Various clinical variables associated with ischemic stroke during the neonatal period have been reported, including prothrombotic states, acute systemic illness, infection, cardiopathy, maternal and obstetric factors, and placental pathology.[8,19–21] It is considered that ischemic perinatal stroke is a multiple-risk problem.[8] However, in a significant number of neonates, provoking factors are not evident.[20] Most studies on NAIS have been limited by modest sample sizes and heterogeneous study populations. Because data are limited, treatment concepts are still not evidence based. The International Pediatric Stroke Study (IPSS) is a multicenter collaboration that aims to develop standardized protocols enabling data collection on diagnosis, investigation, treatment, and outcome assessment of children with stroke. The IPSS recently reported multicenter data from 248 neonates with a diagnosis of NAIS.[20] Their findings confirmed results from previous smaller studies concerning manifestation, associated clinical variables, and infarct characteristics. Specifically, symptoms of NAIS were nonspecific, and seizures were the most common symptom. Most infants presented with isolated lesions in anterior circulation. Lesions were more commonly left-sided.[20] The Swiss Neuropediatric Stroke Registry (SNPSR), a prospective, multicenter pediatric cohort, began in 2000 and joined the IPSS in 2011.[22] Therefore, the 2011 IPSS report on NAIS did not include data from the SNPSR.[20] The primary aim of the current study was to report the incidence of NAIS (excluding fetal ischemic stroke or PPIS) in Switzerland over an 11-year study period (between 2000 and 2010). Additionally, we aimed to provide an overview of NAIS's clinical manifestation, infarct characteristics, associated clinical variables, treatment strategies, and outcomes.

METHODS

Participants and Data Collection

The SNPSR is a prospective, population-based registry aiming to collect data on symptoms, clinical findings, associated clinical variables, vascular distribution, laboratory investigations, and treatments for symptomatic childhood stroke in Switzerland (children <16 years with arterial ischemic stroke and cerebral sinus venous thrombosis).[22] The SNPSR is a nationwide cooperative and was approved by the local ethics board and by the Swiss Federal Ministry of Health. Its study center is located at the University Children's Hospital in Bern. For the current study, neonates with a diagnosis of NAIS (symptomatic at presentation, diagnosed during the first 28 days of life, and confirmed by neuroimaging on computed tomography or MRI) and registered in the SNPSR between January 2000 and December 2010 were included. Patients with purely hemorrhagic stroke, retrospectively diagnosed cases (PPIS), and infants born before 36 weeks' gestation were excluded. In Switzerland, neonates with a diagnosis of NAIS are usually transferred to dedicated care centers under the common care of a pediatric neurologist and a neonatologist. Long-term follow-up is generally assumed by the neurologist. Thus, to collect systematic, prospective data on all new cases, each of the 14 neuropediatric centers (covering all of Switzerland) was contacted every month by e-mail. In addition, an e-mail was addressed to the 16 Swiss neonatal units with the request that they report known cases using obligatory return forms. The units were requested to answer, even if they had no patient during the period. If no answer was obtained, the units were contacted again, first by e-mail, and if there was no reply, by phone. For every registered case, the reporting centers were

TABLE 1 Epidemiologic Studies Concerning NAIS

Authors	Date	Type of Registry	Description	Registration	Cases	Incidence of NAIS and PPIS per 100 000 Live Births	Ages
Perlman et al[18]	1994	Hospital-based	Retrospective analysis of hospital records, United States of America	Acutely (NAIS)	NAIS: 8	NAIS: 29	All gestational ages
Estan and Hope[17]	1997	Hospital-based	Retrospective analysis of hospital records, United Kingdom	Acutely (NAIS)	NAIS: 11	NAIS: 25	>31 wk
Govaert et al[16]	2000	Hospital-based	Retrospective analysis of ultrasound and MRI records, the Netherlands	Acutely (NAIS)	NAIS: 40	NAIS: 35	All gestational ages
Lynch et al[15]	2002	Population-based	National Hospital Discharge Survey, United States of America	Acutely (NAIS)	NAIS: NA	NAIS: 18	All gestational ages
Wu et al[2]	2004	Population-based	Electronic search for diagnosis within the Kaiser Permanente Medical Care Program birth cohort database, qualifying diagnoses by chart review, United States of America	Acutely (NAIS) and retrospectively (PPIS)	NAIS and PPIS: 38 NAIS: 12 PPIS: 26	NAIS and PPIS: 17 NAIS: 5 PPIS: 12	>36 wk
Lee et al[14]	2005	Population-based	Electronic search of head MRI and computed tomography reports, within the Kaiser Permanente Medical Care Program birth cohort database, United States of America	Acutely (NAIS) and retrospectively (PPIS)	NAIS and PPIS: 40 NAIS: 23 PPIS: 17	NAIS and PPIS: 20 NAIS: 12 PPIS: 8	All gestational ages
Schulzke et al[13]	2005	Hospital-based	Retrospective analysis of hospital records, Switzerland	Acutely (NAIS)	NAIS: 5	NAIS: 43	All gestational ages
Laugesaar et al[12]	2007	Population-based	Retrospective analysis of hospital records; prospective registration of new cases (partly); inquiry among child neurologists and general practitioners; Estonia	Acutely (NAIS) and retrospectively (PPIS)[a]	NAIS: 4	NAIS: 7	All gestational ages
Tuckuviene et al[10]	2011	Population-based	Electronic search of the Hospital Discharge Database of the Danish National Patient Registry, Denmark	Acutely (NAIS)	NAIS: 52	NAIS: 6	All gestational ages
Present study		Population-based	Prospective registration by the SNPSR via inquiry among child neurologists and neonatologists	Acutely (NAIS)	NAIS: 100	NAIS: 12	>36 wk

[a] The study by Laugesaar et al included acutely and retrospectively diagnosed arterial ischemic and hemorrhagic stroke. They reported an overall incidence of 38 cases (12 were diagnosed acutely and 26 retrospectively), with an overall 63 cases per 100 000 live births. Because only 4 neonates had a diagnosis of arterial ischemic stroke in the neonatal period, the true incidence for NAIS was 6.7 cases per 100 000 live births.

asked to report data on symptoms at manifestation, clinical manifestation, localization, vascular distribution, type of stroke, and associated clinical variables. All data were gathered by a research pediatrician associated with the SNPSR. To confirm the diagnosis of NAIS, the SNPSR required a copy of the neuroimaging data, and the images were reevaluated by 3 of the coauthors (L.M., E.B., and M.S.) and one neuroradiologist. The SNPSR did not provide any treatment recommendations. No laboratory investigations were required, but an algorithm for investigations was available.[22] All reported data were entered into the SNPSR database by the research pediatrician.

Outcome Assessment

To gather short-term follow-up data (>3 months until 1 year after the stroke), the SNPSR asked the reporting child neurologist or neonatologist for data on clinical course, type and duration of treatment, and follow-up investigations on a return form. Medium-term outcome assessment

(>1 year after the stroke) was prospectively performed ~2 years after the stroke. It consisted of a structured neurologic and developmental assessment (Bayley Scales of Infant Development, second edition [BSID-II]). Infants who were so severely impaired that structured testing could not be performed were assigned a mental development index (MDI) and psychomotor development index of 49. The SNPSR offered a follow-up examination by a research pediatrician at the reporting study site or at the family's home, if families wished. In some cases, reporting study centers chose to perform outcome assessments at their neurodevelopmental unit. In cases where a standardized assessment by the BSID-II was not available (eg, because of a lack of cooperation from the child), the SNPSR study center asked the reporting physician to provide information on outcomes separately. Additionally, a chart review was performed.

Outcome Definitions

Outcome data were defined as follows: At short-term follow-up, infants with clear clinical signs of hemiplegia or tetraplegia were defined as having motor abnormality. Motor abnormalities at medium-term follow-up were diagnosed according to the guidelines of the Surveillance Group of CP in Europe[23] and classified according to the Gross Motor Functioning Classification Scale (GMFCS).[24] Mental outcomes were classified according to the BSID-II, as follows: MDI of 85 to 114, within normal limits; MDI of 70 to 84, mildly delayed performance; and MDI <70, significantly delayed performance. Use of antiepileptic medication was documented if the child took any antiepileptic drugs at the time of follow-up.

Statistical Analysis

The incidence of NAIS was calculated based on the Swiss population according to the Swiss Federal Statistical Office (http://www.bfs.admin.ch). Poisson rates and proportions were calculated together with their exact 95% confidence intervals (CIs). Exact tests for homogeneity and for trends in Poisson rates were used where appropriate. Results regarding presentation, infarct characteristics, associated clinical variables, coagulation studies, and antithrombotic medication are presented with descriptive statistics. We calculated associations between infarct characteristics and outcomes by using a χ^2 test. SPSS version 21.0 for Windows (IBM SPSS Statistics, IBM Corporation) was used to analyze data.

RESULTS

Study Population and Incidence of NAIS in Switzerland

One hundred neonates were registered in the SNPSR (67 boys; median gestational age, 40.0 weeks [range 36.0–41.9 weeks]; median age at manifestation, 2.0 days [range 1–26 days]; median birth weight, 3380 g [range 2370–4520 g]). During the study period the Swiss Federal Statistical Office reported 824 090 live births. Ninety-three percent (769 508) were born at ≥36 weeks' gestational age Thus, over the complete study period, the incidence of NAIS in Switzerland was 13 (95% CI, 11–16) per 100 000 live births, with a significantly higher incidence in boys (17 per 100 000 live births; 95% CI, 13–21) than in girls (9 per 100 000 live births; 95% CI, 6–12; P = .002). There was no significant trend in the incidence over time (see Fig 1).

Presentation

Information about manifestation was available for 96 neonates. All but 3 (97%) presented with seizures, 31 (32%) presented with tone abnormalities (increased or decreased muscle tone), 17 (18%) with respiratory symptoms, 11 (11%) with movement abnormalities (abnormal spontaneous movements without clear asymmetry), 7 (7%) with hemiparesis, 7 (7%) with decreased level of consciousness, and 5 (5%) with irritability. Fifty (52%) had seizures as the only presenting symptom.

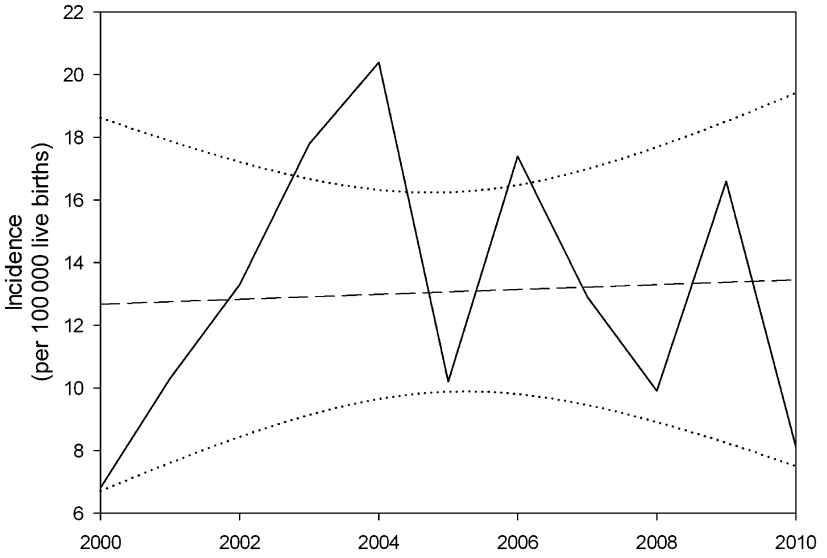

FIGURE 1

Overall incidence of neonatal ischemic stroke in Switzerland over an 11-year period. The solid black line represents the incidence per 100 000 live births; the dotted lines encompass the 95% confidence interval; and the dashed line represents the regression line. Incidence remained stable over time (exact test of trend in Poisson rates: P = .85).

Infarct Characteristics

Table 2 provides an overview of the infarct characteristics. Infarcts were predominantly unilateral (81%) and left-sided (80% of unilateral infarcts). Eighty-nine percent showed involvement of the anterior circulation only (internal carotid artery, anterior cerebral artery, middle cerebral artery), whereas 11% showed combined lesions in anterior and posterior circulation (vertebral artery, basilar artery, posterior cerebral artery). No cases of isolated posterior circulation stroke were observed.

Associated Clinical Variables and Genetic Testing for Thrombophilia

Table 3 lists the associated clinical variables and the results of genetic testing for thrombophilia. Associated clinical variables were classified into 3 subcategories (maternal conditions, birth complications, and neonatal comorbidities). Maternal conditions were reported in 30 neonates (32%), birth complications in 64 (68%), and neonatal comorbidities in 52 (54%). For 31 (32%) neonates $\geq$1 associated clinical variable was observed in 1 subcategory; for 27 (28%), associated clinical variables were observed in 2 subcategories; and for 20 (21%), associated clinical variables were observed in all 3 subcategories. In 16 neonates (16%), no associated clinical variable was noted. Although the SNPSR suggested coagulation studies, the laboratory investigations of these neonates either were not systematically performed or were done in distinct local laboratories with inconsistent normative neonatal values. We therefore report only the results of genetic testing not subject to biases. These showed heterozygous factor V Leiden mutation in 5% (N = 3), heterozygous prothrombin G20210A mutation in 11% (N = 6), heterozygous methylene tetrahydrofolate reductase mutation in 36% (N = 10), and homozygous methylene tetrahydrofolate reductase mutation in 4% (N = 1) of the assessed cases.

Antithrombotic and Antiplatelet Medication

Information about treatment was available for 95 neonates. Sixteen (17%) received antithrombotic or antiplatelet medication (12 [13%] acetylsalicylic acid, 3 [3%] unfractionated heparin, 5 [5%] low molecular weight heparin, and 1 [1%] thrombolytic therapy; 4 received >1 drug). The neonate receiving thrombolytic therapy had an additional thrombosis of the inferior vena cava, which was the indication for thrombolysis. No serious side effects were reported.

Outcomes

Two neonates died, both from cardiorespiratory insufficiency not related to the stroke: 1 because of transposition of the great arteries and 1 after surgical correction of esophageal atresia. Information on short-term follow-up was available for 87 cases (89% of survivors; median 6.0 months, range 3–12 months). Seventy-four patients (76% of survivors) were seen at medium-term follow-up (median 24.0 months, range 12–38 months). No clinical recurrence of stroke was reported. Details regarding outcome are provided in Table 4. At medium-term follow-up, 29 children (39%) had a diagnosis of CP. The BSID-II was performed in 62 children (mean MDI 91.5, SD 18.7). Forty-three (69%) showed an MDI within normal limits, 13 (21%) had mildly delayed performance, and 6 (10%) showed significantly delayed performance. In 12 children, no BSID-II was performed because of lack of cooperation. According to chart review, 3 of these had mild retardation of language development, and 9 showed normal development. Antiepileptic medication at short-term follow-up was documented in 17 infants (19%) and had been discontinued in 11 by medium-term follow-up. Six children developed symptomatic epilepsy at medium-term follow-up. In addition, 1 patient not receiving antiepileptic medication at short-term follow-up received it at medium-term follow-up. Thus, 7 (9%) were treated for epilepsy at medium-term follow-up. Among them, 4 had infantile spasms. Table 5 shows the associations between infarct characteristics, GMFCS levels, results of the BSID-II, and antiepileptic medication use at medium-term follow-up. Patients with bilateral lesions were more likely to be treated for epilepsy, have higher GMFCS scores, and have poorer BSID-II results.

TABLE 2 Infarct Characteristics

	Unilateral			Bilateral
	Left	Right	All	
Total (n = 100)	65 (65%)	16 (16%)	81 (81%)	19 (19%)
Only anterior circulation (n = 89)	64 (64%)	14 (14%)	78 (78%)	11 (11%)
Anterior and posterior circulation (n = 11)	1 (1%)	2 (2%)	3 (3%)	8 (9%)
Hemorrhagic involvement (n = 24)	14 (14%)	7 (7%)	21 (21%)	3 (3%)

DISCUSSION

The principal aim of the current study was to report epidemiologic data on the incidence of NAIS in Switzerland. This study provides data from a prospective, nationwide, population-based analysis over an 11-year period. Our observed incidence of 13 per 100 000 live births was stable over time. The reported incidence of NAIS differs widely between studies, possibly because of differences in inclusion criteria, reporting strategies, study duration, frequency of diagnostic procedures in at-risk children, study populations (eg, including or excluding preterm neonates), and health care policies (see Table 1). Epidemiologic data have been provided by 4 hospital-based studies[13,16–18] and 5 population-based studies.[2,10,12,14,15] Hospital-based

TABLE 3 Associated Clinical Variables

Maternal Conditions (n = 94)		Birth Complications (n = 94)		Neonatal Comorbidities (n = 97)		Prothrombotic States (only genetic tests) of the Child		
Premature rupture of the membranes	8 (9%)	Forceps	3 (3%)	Mechanical ventilation	15 (15%)	Factor V Leiden	Het 3/58 (5%)	Hom 0/58
Abnormal placenta	3 (3%)	Birth asphyxia	15 (16%)	Neonatal infection	26 (27%)	Methylene-tetrahydrofolate-reductase mutation	Het 10/28 (36%)	Hom 1/28 (4%)
Thrombocytopenia	5 (5%)	Neonatal resuscitation	3 (3%)	Meningitis or encephalitis	2 (2%)	Prothrombin G20210A	Het 6/56 (11%)	Hom 0/58
Other	16 (17%)	Pathologic cardiotocography	28 (30%)	Hypoxic ischemic encephalopathy	3 (3%)	—	—	—
	—	Meconium-stained amniotic fluid	19 (20%)	Hypoglycemia	6 (6%)	—	—	—
	—	1-min Apgar score ≤5	18 (19%)	Arterial hypotonia	6 (6%)	—	—	—
	—	5-min Apgar score ≤5	4 (4%)	Thrombosis	5 (5%)	—	—	—
	—	10-min Apgar score ≤5	1 (1%)	Obstetric plexus brachialis lesion	2 (2%)	—	—	—
	—	—	—	Anemia	3 (3%)	—	—	—
	—	—	—	Other	13 (13%)	—	—	—

Het, heterozygous; Hom, homozygous.

approaches may overestimate a condition's incidence in the general population because of referral biases, and population-based studies may underestimate it because of missing cases. Hospital-based studies report a higher incidence of NAIS than do population-based studies.[13,16–18] Three of the population-based studies included NAIS (presentation during the neonatal period) and PPIS (diagnosed retrospectively).[2,12,14] Two population-based studies included only NAIS.[10,15] To allow a comparison with the current study, only cases with NAIS should be considered (Table 1). The estimated incidence of NAIS (symptoms appearing during the neonatal period) in a population-based setting is thus between 5 and 18 cases per 100 000 live births.

Similar to other studies, we observed NAIS more commonly in boys. The exact mechanisms regarding gender and hormone interactions in stroke in adults, children, and neonates are not yet understood, but boys and men have a higher incidence of stroke throughout much of the life span.[25] Higher birth weight might increase susceptibility to NAIS.[26] Fetal gender may affect maternal hemodynamics.[27] Children and neonates show elevated testosterone levels, which increases the odds of cerebral thromboembolism.[28] Cell death pathways in response to ischemia are also influenced by gender.[25] The majority of patients in our study had unilateral lesions in anterior circulation on the left side, consistent with populations in previous studies.[2,14,20] Anatomic settings and variable vulnerability to ischemic lesions might explain why the left side is more commonly involved.[27,29]

We found NAIS to be associated with maternal conditions, birth complications, and neonatal comorbidities. Clinical variables associated with NAIS were comparable to those in other studies.[14,19,30] We did not include

TABLE 4 Follow-up Results

Short-term follow-up	
Age	Mean 6.12 mo (SD 2.1 mo)
Died (not related to stroke)	2 (2%)
Lost to follow-up	11 (11%)
Follow-up available	87 (89% of survivors)
Motor abnormality	35/87 (40%)
Unilateral spastic movement disorder	31/87 (36%)
Bilateral spastic movement disorder	4/87 (4%)
Antiepileptic medication	17/87 (19%)
Antiepileptic medication discontinued thereafter	11/87 (12%)
Antiepileptic medication continued	6/87 (7%)
Medium-term follow-up	
Age	Mean 23.3 mo (SD 4.3 mo)
Died (not related to stroke)	2 (2%)
Refused participation	4 (4%)
Moved to foreign country	1 (1%)
Lost to follow-up	20 (20%)
Follow-up available	74 (76% of survivors)
Cerebral palsy	29/74 (39%)
Unilateral spastic cerebral palsy	23/74 (31%) (all GMFCS I–II)
Bilateral spastic cerebral palsy	4/74 (5%) (all GMFCS III–V)
Ataxic cerebral palsy	2/74 (3%) all GMFCS I or II)
BSID-II MDI (n = 62)	Mean 91.5 (range 49–119, SD 18.7)
Normal performance (MDI 85–115)	43/62 (69%)
Mildly delayed performance (MDI 70–84)	13/62 (21%)
Significantly delayed performance (MDI <70)	6/62 (10%)
Epilepsy	7/74 (9%)
Antecedent of infantile spasms	4/74 (5%)
Symptomatic epilepsy with focal or generalized seizures	3/74 (4%)

TABLE 5 Associations Between Stroke Characteristics and Follow-up Data

	No CP	GMFCS I–II	GMFCS III–V	*P*
Unilateral lesion	37	21	0	<.001
Bilateral lesion	8	4	4	
Only anterior circulation	42	22	2	.027
Posterior circulation involved	3	3	2	
MDI >85	30	13	0	<.001
MDI 70–84	6	7	0	
MDI <70	0	2	4	
No epilepsy	45	21	1	<.001
Symptomatic epilepsy	0	4	3	
	MDI >85	MDI 70–84	MDI <70	*P*
Unilateral lesion	38	10	0	<.001
Bilateral lesion	5	3	6	
Only anterior circulation	40	13	3	.002
Posterior circulation involved	3	0	3	
No CP	30	6	0	<.001
GMFCS I–II	13	7	2	
GMFCS III–V	0	0	4	
No epilepsy	42	11	2	<.001
Symptomatic epilepsy	1	2	4	
	No Epilepsy		Symptomatic Epilepsy	*P*
Unilateral lesion	55		3	.016
Bilateral lesion	12		4	
Only anterior circulation	61		5	.112
Posterior circulation involved	6		2	
No CP	45		0	<.001
GMFCS I–II	21		4	
GMFCS III–V	1		3	
MDI >85	42		1	<.001
MDI 70–84	11		2	
MDI <70	2		4	

a control group, and so no causative conclusions can be drawn. Current guidelines for treating NAIS are consensus based.[31] In our study, the use of antithrombotic and antiplatelet therapy was low (17%). No serious side effects were reported. Similar to Kirton et al,[20] we observed differing treatment strategies between single centers. The current study does not support conclusions about the benefits of antithrombotic and antiplatelet treatment.

Two years after the stroke, CP was diagnosed in 39% of patients. Other studies found CP in 26% to 68%.[5,6,32,33] Different motor outcomes between studies can be explained by differences in functional measures, follow-up duration (patients with milder motor impairment might been missed), and methodological aspects (studies including only NAIS show motor problems less often than studies including PPIS because, by definition, this group frequently presents with motor problems). About one-third of patients showed delayed mental performance at the 2-year follow-up, in accordance with previous research,[34] but this proportion should not be overestimated. Early assessments are not necessarily good predictors of intellectual outcomes at school.[35] Longer-term follow-up is necessary to determine the effect of "growing into deficit" and thus the long-term impacts of NAIS on cognition.

Nine percent of the patients were treated with antiepileptic drugs at medium-term follow-up, less frequently than in other studies.[36,37] Treatment strategies for seizures after NAIS may differ between centers. As previously reported,[5,33] poor motor outcomes were more common in patients with bilateral stroke, as was treatment with antiepileptic drugs. A previous study found stroke size to relate to later seizure activity.[36]

Limitations

Expertise in neonatology, child neurology, neuroradiology, and related

areas differs by center. However, reported cases were reviewed by our study coordinators; thus, we believe overestimation probably did not occur in our study. The unique sources of the SNPSR are the reporting study centers. Quality control methods, including other sources of data, were not available. In Switzerland, neonates with signs of stroke are systematically referred to neonatal units with expertise in pediatric neurology. Still, an underestimation of the incidence of NAIS cannot be ruled out. The increase in incidence over the first years could suggest an accumulation effect.

The BSID-II was not performed in all patients, primarily because of lack of cooperation. Although the BSID-II is a standardized outcome assessment, it was not performed by the same examiner during the study period, which may represent bias. The GMFCS is heavily weighted on lower extremity function and walking and therefore may not be relevant to patients with NAIS. Future studies therefore should focus more on upper extremity function.

Neuroimaging findings were not described in detail in this study. More specific analyses (eg, volume of lesion, affected territory) might increase neuroimaging's prognostic value. We therefore plan to perform a more detailed analysis, including a detailed description of the observed lesions and their effects on outcomes. Information about epileptic seizures during follow-up should be interpreted with caution, because details about treatment, electroencephalography findings, and type of seizures were not assessed prospectively.

CONCLUSIONS

Our study on NAIS in Switzerland shows a similar incidence to other population-based studies but a lower incidence than hospital-based studies. The current study does not support conclusions about the benefits of antithrombotic and antiplatelet treatment. About one-third of our patients developed CP, and about one-third showed delayed mental performance 2 years after the stroke. Children with normal mental performance may later exhibit deficits.

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