

Delayed diagnosis of acute ischemic stroke in children – a registry-based study in Switzerland

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Summary

QUESTIONS UNDER STUDY/PRINCIPLES: After arterial ischemic stroke (AIS) an early diagnosis helps preserve treatment options that are no longer available later. Paediatric AIS is difficult to diagnose and often the time to diagnosis exceeds the time window of 6 hours defined for thrombolysis in adults. We investigated the delay from the onset of symptoms to AIS diagnosis in children and potential contributing factors.

METHODS: We included children with AIS below 16 years from the population-based Swiss Neuropaediatric Stroke Registry (2000–2006). We evaluated the time between initial medical evaluation for stroke signs/symptoms and diagnosis, risk factors, co-morbidities and imaging findings.

RESULTS: A total of 91 children (61 boys), with a median age of 5.3 years (range: 0.2–16.2), were included. The time to diagnosis (by neuro-imaging) was <6 hours in 32 (35%), 6–12 hours in 23 (25%), 12–24 hours in 15 (16%) and >24 hours in 21 (23%) children. Of 74 children not hospitalised when the stroke occurred, 42% had adequate outpatient management. Delays in diagnosis were attributed to: parents/caregivers (n = 20), physicians of first referral (n = 5) and tertiary care hospitals (n = 8). A co-morbidity hindered timely diagnosis in eight children. No other factors were associated with delay to diagnosis. A total of 17 children were inpatients at AIS onset.

CONCLUSIONS: One-third of children with AIS were diagnosed within six hours. Diagnostic delay was predominantly caused by insufficient recognition of stroke symptoms. Increased public and expert awareness and immediate access to diagnostic imaging are essential. The ability of parents/caregivers and health professionals to recognise stroke symptoms in a child needs to be improved.

Key words: acute ischemic stroke; diagnosis; children; time lag; population-based registry

Introduction

Arterial ischemic stroke (AIS) in adults is considered a serious health threat and requires urgent medical treatment. Prompt diagnosis allows the therapeutic option of thrombolysis within the time window of 3 to 6 hours after first symptoms. Alternatively, early anti-platelet therapy is effective in improving the outcome after stroke [1, 2]. Paediatric AIS has severity and long-term outcomes similar to those in young adults [3]. Two-thirds of children sustaining AIS have neurological deficits that may result in life-long disability, thus critically impacting their potential development [4–7]. Therefore, early diagnosis and treatment is as important in children as it is in adults.

The diagnosis of stroke depends on the suspicion of stroke by lay persons and health professionals, and careful clinical examination. In children, an early diagnosis is more difficult for several reasons: firstly, AIS is less frequent than in adults. Population-based estimates of the incidence of paediatric AIS range from 2 to 5 per 100,000 children/year [5, 8], which is rare compared to the incidence of 264 per 100,000 adults/year [9]. Secondly, most parents are unaware of possible stroke symptoms in children and health professionals rarely consider stroke in their differential diagnosis [10]. In the diagnostic work-up for children with suspected stroke, other health conditions such as postictal state, hemiplegic migraine and acute demyelinating encephalomyelopathy have to be considered [11]. Paediatric stroke is more difficult to diagnose because the aetiology and risk factors of stroke in children are very heterogeneous and differ from those in adults [5, 12].

In adult stroke, considerable efforts have been made for early diagnosis and treatment [13–17]. Information campaigns aim at educating the general population to the signs and symptoms of stroke in order to shorten the delay in seeking medical help and reduce the severity of resulting disability. Furthermore, emergency and acute care have improved, for example by establishing specialised stroke units which may also be beneficial in reducing delays to diagnosis and the treatment of stroke.

Recent reports from different countries and health systems have confirmed delays in the diagnosis of childhood stroke, and also identified a broad range of reasons why this may occur [18–21]. We reviewed the history of early acute care in a representative sample of infants and children who were diagnosed with AIS in Switzerland. The objective was to study the time course of AIS diagnosis in the Swiss healthcare system and to investigate potential determinants of delays in diagnosis.

Methods

Data source

We retrospectively analysed a comprehensive set of data of children with AIS who were registered in the Swiss Neuropaediatric Stroke Registry (SNPSR); a prospective, population-based paediatric stroke registry in Switzerland which has been in operation since the year 2000. Methods of data collection have been described elsewhere [5]. In brief, cases of children with a diagnosis of AIS were continuously identified by licensed neuropaediatricians in hospitals and private practices in Switzerland. AIS was defined as 1) a focal neurological deficit of acute onset and 2) confirmation of the diagnosis by computerised tomography (CT) scans or magnetic resonance imaging (MRI) showing infarction determined by localisation of a lesion that is consistent with the neurological signs and symptoms. Data on patient characteristics, clinical parameters, acute care, and follow-up were reported anonymously to the SNPSR study centre at the Children's University Hospital, Bern, Switzerland. The SNPSR was approved by the local ethics board of the Canton of Bern, Switzerland, and by the Swiss Federal Ministry of Health.

Study population

We included infants and children aged 1 month to 16 years residing in Switzerland and diagnosed with AIS in one of the participating thirteen medical centres between January 1st, 2000 and December 31st, 2006. We excluded children with stroke in the perinatal or neonatal period up to 30 days after birth.

Study data

Information extracted from the SNPSR dataset and the medical records included: demographic data (sex, age at time of stroke), known risk factors in child's history (e.g. infections, heart disease, head injury and migraine), risk factors in the family history (e.g. first degree relative with stroke, heart attack or thrombosis), clinical presentation of AIS as signs and symptoms (e.g. decreased consciousness, headache, seizures, other sensory motor deficit, visual problems / palsy of cranial nerves, aphasia, ataxia), type of diagnostic imaging performed, and localisation of stroke. Based on these data, we calculated the paediatric National Institute of Health Stroke Scale (pedNIHSS) score. This score reflects several brain functions including consciousness, vision, sensation, movement, speech and language, with values ranging between 0 (no symptoms) and 42 (most affected) [22].

We extracted additional procedural information from the medical charts: first contact with the healthcare system (doctor in private practice, peripheral hospital, central hospital with stroke specialist, or child already hospitalised at time of AIS), reason for delay (inadequate approach to diagnosis judged retrospectively by reviewing the chart notes with a critical assessment of each step to diagnosis even if within 6 hours) caused by parents (not seeking help immediately), delay by physician in private practice or by hospital-based physician (not attributing the necessary emergency for further investigations), or in-patients with a condition masking AIS symptoms or signs (e.g. after cardiovascular surgery, or with severe autoimmune disease).

The primary outcome was a delay in AIS diagnosis defined as 6 or more hours elapsed between time of onset of AIS symptoms (based on the oral history taken from the parent/caregiver or child) and time of diagnosis (defined as time of CT scan or MRI confirming AIS diagnosis). Due to the imprecision in reporting the onset of symptoms, the time intervals were grouped as the following: <6 hours, 6–12 hours, 12–24 hours, 24–48 hours and >48 hours.

Data analyses

After the medical record review for all study participants and based on our observations and experience with typical clinical pathways of children diagnosed with paediatric stroke, we extracted several additional variables that may be associated with delays in AIS diagnosis: age at time of stroke, sex, key stroke symptoms (hemiparesis, dysphasia and seizure), number of different localisations of cerebral lesions, cortex involvement, cerebral hemisphere of stroke, pedNIHSS, type of first contact with medical sector, and use of CT scan for diagnosis.

We used descriptive statistics to characterise the study population as appropriate. Exploratory analyses using Pearson's χ^2 test and univariate logistic regression models were

conducted to identify factors that may potentially explain inadequate management. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using STATA Version 11 (Stata Corporation, College Station, TX USA).

Results

Patient characteristics and clinical presentation

We identified the records of 91 children who met the inclusion criteria. A total of 61 boys and 30 girls with a median age of 5.3 years (range 0.2 to 16.2) were included. Patient characteristics, clinical presentation and known risk factors are given in table 1.

The most frequent stroke symptom was a sensory motor deficit including hemiparesis (table 1). For 74 (81%) children, parents/caregivers reported a sensory motor problem in the medical history and in 78 (86%) it was found or confirmed upon clinical examination. In 41 (45%) children it was combined with dysphasia or aphasia. A change of level of consciousness was reported in 32 (35%) children and was still present at the time of clinical examination in 22 (24%). Ataxia was reported in four children and confirmed by clinical examination in 12 (13%). A total of 16 children (18%) had experienced a seizure. The pedNIHSS at time of admission ranged from 0 (no stroke symptoms) to 27 (severe stroke); the median was 6 (moderate stroke).

All children underwent diagnostic imaging procedures to confirm diagnosis. A total of 49 of the 54 CT scans (91%) and all of the 72 MRI investigations confirmed the in-

farction (table 2). In four children with normal CT scan findings, the infarction was proven by MRI. A total of 35 (38%) children underwent both diagnostic procedures, most of them within the same 24 hours. In one child with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes syndrome (MELAS), the CT scan was normal and MRI could not be performed due to the presence of a cardiac pacemaker. A total of 38 (42%) children had lesions of the left cerebral hemisphere, 38 (42%) had lesions of the right, and 15 (16%) had bilateral AIS. In total, 47 (52%) children had a single anatomical lesion, 39 children (43%) had two and five children (5%) had three lesions. The most frequent single localisation was in the cortex (32%). Lesions in the cortex, the basal ganglia or both accounted for 67 (74%) of all infarctions (table 3).

Time to diagnosis and diagnostic pathways

In only one-third of children (32 of 91) the diagnosis of AIS was made within the first 6 hours after the onset of first symptoms. More detailed information is given in table 4. Of the 74 children not hospitalised at the time of first symptoms, 31 (42%) had adequate outpatient management. In eight of these children, the delay until diagnosis was longer than 6 hours, due to the time needed for transportation to a diagnostic centre for example.

For 43 children (58%) not hospitalised at the time of first symptoms outpatient management was regarded as inadequate in retrospect. The initial contact was with a physician in private practice in nine of these children (21%), with a peripheral hospital in 16 (37%) children, and with

Table 1: Patient characteristics and clinical presentation.

		N (%)
Age at time of stroke	≤6.0 years	48 (53)
	6.1–12.0 years	23 (25)
	>12.0 years ^a	20 (22)
Median age (years)(range)	5.3 (0.2–16.2)	
Sex	Male	61 (67)
	Female	30 (33)
Risk factors in child's medical history ^b	Prior neurological problems ^e	35 (38)
	Other infection ^c	24 (26)
	Heart disease	13 (19)
	Varicella	13 (14)
	Head trauma	12 (13)
	Migraine	8 (9)
	Systemic disease ^d	8 (9)
Risk factors in family medical history	In first-degree relative(s)	30 (33)
	In other relative(s)	16 (18)
Clinical presentation as symptom from history / as sign confirmed upon medical examination ^b (% given for higher n)	Sensory motor deficit (incl. hemiparesis)	74 /78 (86)
	Aphasia or dysphasia	35/41 (45)
	Change of level of consciousness	32/22 (35)
	Headache	25 (27)
	Visual problem	9/11 (12)
	<i>incl. palsy of cranial nerve III, IV, VI</i>	
	Ataxia	4 /12 (13)
	Emesis	19 (21)
	Palsy of facial nerve	8/12 (13)
	Seizures	16 (18)

N = number of study participants;

*

^a 16 years of age was study inclusion cut-off

^b multiple listings possible

^c includes upper respiratory tract and ENT infections, undetermined fever

^d includes haematological and autoimmune diseases

^e prior neurological problems as developmental delay, speech delay, attention deficit disorder, epilepsy, meningitis or encephalitis

a tertiary care hospital in 13 (30%) children. For 5 (12%) children, the initial contact could not be determined in retrospect. These five children were excluded from this specific statistical analysis (see below).

In 20 (47%) of these 43 children, the delay occurred before the first contact with a healthcare provider, therefore either by the child's parents or caregiver. In half of these children it was more than 24 hours. In five of 43 children (12%) the delay was attributed to the management by a physician in private practice or a peripheral hospital, including delayed transfers to tertiary hospitals. In eight children (19%) the delayed diagnosis was made after admission to a tertiary care hospital; for half of these children the delay exceeded 24 hours. A total of eight (19%) children suffered from a systemic disease and this may explain why the primary management of AIS was not optimal. In the two remaining cases, the circumstances of AIS diagnosis were not documented sufficiently to decide at which stage the management was inadequate. These last 10 children were not included into statistical analyses seeking for contributing factors of inadequate management by parents or health care professionals.

A total of 17 children (19% of all 91 children) were already hospitalised for other reasons when AIS occurred. The AIS diagnosis was made within the first 6 hours in only five of these children and the delay exceeded 24 hours in four

children (table 4). Since these children had been admitted for a variety of reasons and the diagnosis was reached with different approaches, they were excluded from the statistical analyses. Furthermore, due to the small number in this group separate statistics were not considered.

Delays of diagnosis and associated factors

Univariate analyses revealed that none of the following potential determinants were associated with adequate or inadequate management by parents or doctors: age ($p = 0.551$), sex ($p = 0.205$), hemiparesis ($p = 0.198$), dysphasia ($p = 0.305$), seizure ($p = 0.805$), number of distinct localisations of cerebral lesions ($p = 0.967$), cortex involvement ($p = 0.384$), cerebral hemisphere of stroke ($p = 0.658$), and pedNIHSS ($p = 0.512$). Furthermore, neither type of first contact with medical sector ($p = 0.079$) nor the use of CT scan for diagnosis ($p = 0.311$) were associated with delay of diagnosis. For the three key symptoms hemiparesis, dysphasia and seizure we repeated the analysis in the subgroup of 27 children aged 6 years or older but did not identify any association with delay of diagnosis in this subgroup. No multivariable analyses were performed.

Table 2: Initial diagnostic imaging in 91 children with acute ischemic stroke: comparison of results of CT scan and MRI.

CT scan finding	MRI finding			Total number
	Normal	Abnormal	Not performed	
Normal	0	4	1	5
Abnormal	0	31	18	49
Not performed	0	37	0	37
Total N	0	72	19	91

Normal: no sign of ischemic lesion in any sequence of the imaging
Abnormal: ischemic lesion in at least one sequence of the imaging

Table 3: Localisation of lesion in diagnostic imaging.

Localisation	Structure	Number (%)
Supratentorial localisation only: N = 81	Cortex	30 (32)
	Cortex and basal ganglia	28 (31)
	Basal ganglia	9 (10)
	Thalamus	5 (5)
	Cortex and thalamus	5 (5)
	Cortex, basal ganglia, thalamus	4 (4)
Infratentorial localisation only: N = 3	Cerebellum	2 (2)
	Brain stem	1 (1)
Combined supra- and infratentorial localisation: N = 7	Cortex, and brainstem	3 (3)
	Cortex, brainstem, basal ganglia	1 (3)
	Cortex and cerebellum	3 (3)

Table 4: Delays in diagnosis and diagnostic management.

	Time diagnosis (hours)					Total N
	<6	6–12	12–24	24–48	>48	
Not hospitalised at time of stroke	27	17	13	9	8	74
Adequate management	23	6	2	0	0	31
Inadequate management						43
Parents	0	5	5	5	5	20
Physician in private practice / peripheral hospital	1	1	1	1	1	5
Physician in tertiary care hospital	1	1	2	3	1	8
Systemic disease	2	3	2	0	1	8
Unknown reason	0	1	1	0	0	2
Hospitalised at time of stroke	5	6	2	2	2	17
Total number	32	23	15	11	10	91

Discussion

We analysed the diagnostic pathway of a representative sample of children with AIS, focusing on those who were not hospitalised when the stroke occurred. In more than half of these children, the steps taken by parents or healthcare providers from the onset of first symptoms until proper diagnosis of AIS were judged as inadequate and thus, delaying diagnosis. Consequently, in most children the diagnosis would not have been early enough to allow a thrombolytic intervention within the first six hours after AIS. The reasons for delay were diverse but typically included underestimation of the severity of the disease by the parents or healthcare providers of first or second referral. We did not identify any specific demographic or clinical factor associated with a delay of diagnosis. In eight children, a severe co-morbidity led to a delay in the diagnosis of stroke but the approach to diagnosis by parents or healthcare providers was deemed adequate. In most of these children symptoms of the underlying disease were masking symptoms of stroke or symptoms of stroke were difficult to be separated from symptoms of the underlying disease. About two-thirds of the children were already hospitalised at the time of stroke and had a diagnostic delay of more than six hours. This was mainly due to particular circumstances. For instance, a child admitted to an intensive care unit was sedated/relaxed for mechanical ventilation and a proper assessment of cerebral function was very limited. The observation that two-thirds of the children were boys is well known, but so far remains an unexplained fact in the paediatric stroke population [5, 23].

Recently, studies conducted in Great Britain [19], Canada [20] and Australia [21] have analysed delays in diagnosing AIS in children. Our results are comparable to those of the study conducted in Great Britain [19]: the proportion of AIS detected in the first six hours was 28% compared to 35% in our sample. AIS diagnosis was delayed by 24 hours or more in 28% of cases, compared to 23% in Switzerland. In the studies conducted in Australia [21] and Canada [20] the delays were longer. In Australia only 7% of AIS diagnoses were made within three hours, while half took more than 24 hours. The latter was consistent with findings from Canada [20]. These differences might be due to geography and the healthcare systems in these countries. Both the Australian and the Canadian data were collected in medical centres with large catchment areas. Thus, the reason for delay might be partially due to the time needed for transfer to the tertiary care hospital.

The proportion of children not hospitalised at time of stroke was larger in our study (81%) compared to the Canadian study (63%) and the Australian study (60%). However in our population, inpatients did not have shorter diagnostic delays than outpatients. For both groups, about one third of patients were diagnosed within 6 hours. This finding suggests that an important factor for early diagnosis is the awareness of parents, caregivers and healthcare professionals that a child's symptoms or signs may stem from stroke. In our study, most delays occurred at an early stage, that is when parents decided to seek medical advice. In addition to improving the diagnostic work-up for AIS in the healthcare setting, it is thus important to raise the awareness for

childhood stroke in the general population, and in particular, in parents and other caregivers. Lack of awareness of stroke symptoms has been identified as a modifiable cause of delay in the diagnosis of adult stroke [14, 16].

Another important difference between the Canadian and Swiss healthcare setting was the availability of MRI for AIS diagnosis. In the Canadian study, 96% of the children had a CT scan for initial diagnostic imaging, although it led to AIS diagnosis in only 53%. In our study, 59% of the children had an initial CT scan and 38% underwent both diagnostic procedures, most of them with a short time interval between them. These data support the assumption that immediate availability for MRI might improve early diagnosis of stroke.

Stroke severity was however similar in the Canadian and Swiss study with a median pedNIHSS of 7 and 6, respectively. In the Canadian study, pedNIHSS and other factors such as decreased consciousness, focal symptoms, and abrupt onset of symptoms were associated with delay in diagnosis. Similarly, the presence of focal signs was associated with delayed time to diagnosis in the Australian study. We were unable to identify any such relationship in our study. The lack of statistical association between factors such as stroke severity and symptoms and delay in diagnosis might be due to the small number of children included in our study. However, the fact that the Canadian and Australian study with more pronounced delays in diagnosis could find such an association, might point to the possibility that awareness of symptoms, like a change of level of consciousness, and focal signs might help to decrease time lag to diagnosis.

Our study has some limitations: due to the retrospective design, we were unable to determine the exact time points when the first stroke symptoms occurred. Consequently, delay to AIS diagnosis could not be used a continuous variable, and instead we used a categorical variable with five groups. In addition, the registry data and information derived from medical records may have led to an underestimation of delays. It was also not possible for us to extract reliable data on the delays occurring in the 17 children already admitted to hospital at the time of AIS. Furthermore, due to the limited sample size, it may not have been possible to attain the statistical power needed to identify any determinants of diagnostic delay.

A strength of the study was that our analysis was based on a comprehensive and population-based study that included children who were admitted to different types of hospitals. Consequently, our findings were most likely not subject to selection bias and could possibly be generalised to similar healthcare systems.

Conclusion

Currently, only one third of children with AIS are diagnosed within a delay of six hours required for early treatment. Our findings indicate the importance to further increase awareness of childhood stroke to ensure timely diagnosis and treatment. Any efforts to raise awareness should target both healthcare professionals who are likely to see children with stroke at an early stage and the general public, particularly parents and other caregivers.

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