Neuroimaging in childhood arterial ischaemic stroke: evaluation of imaging modalities and aetiologies

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LIST OF ABBREVIATIONS

ACA	Anterior cerebral artery
AIS	Acute ischaemic stroke
DWI	Diffusion-weighted imaging
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography

AIM The aim of this study was to describe neuroimaging patterns associated with arterial ischaemic stroke (AIS) in childhood and to differentiate them according to stroke aetiology.
METHOD Clinical and neuroimaging (acute and follow-up) findings were analysed prospectively in 79 children (48 males, 31 females) aged 2 months to 15 years 8 months (median 5y 3mo) at the time of stroke by the Swiss Neuropaediatric Stroke Registry from 2000 to 2006.
RESULTS Stroke was confirmed in the acute period in 36 out of 41 children who underwent computed tomography, in 53 of 57 who underwent T2-weighted magnetic resonance imaging (MRI) and in all 48 children who underwent diffusion-weighted MRI. AIS occurred in the anterior cerebral artery (ACA) in 63 participants and in all cases was associated with lesions of the middle cerebral artery (MCA). The lesion was cortical–subcortical in 30 out of 63 children, cortical in 25 out of 63, and subcortical in 8 of 63 children. Among participants with AIS in the posterior circulation territory, the stroke was cortical–subcortical in 8 out of 16, cortical in 5 of 16, and thalamic in 3 out of 16 children.
INTERPRETATION AIS mainly involves the anterior circulation territory, with both the ACA and the MCA being affected. The classification of Ganesan is an appropriate population-based classification for our Swiss cohort, but the neuroimaging pattern alone is insufficient to determine the aetiology of stroke in a paediatric population. The results show a poor correlation between lesion pattern and aetiology.

Multiple factors are associated with the risk of paediatric arterial ischaemic stroke (AIS), and there are many trigger factors that provoke an acute event. Specific causes include arteriopathies, cardiac disease, infections, prothrombotic disorders,[1] and cervical arterial dissection.[2,3] Associations between AIS and varicella-zoster virus[4] and severe as well as mild head trauma are also documented. Treatment and prognosis may differ in different subgroups of childhood stroke. Neuroimaging is the first step in diagnosis[5] and, therefore, a correlation between neuroimaging findings and certain aetiologies would be helpful in making further diagnostic and therapeutic decisions. The Trial of Org 10172 in Acute Stroke Treatment classification[6] used for adult stroke has been shown to be inappropriate for classifying childhood AIS because it does not include common paediatric aetiologies such as sickle cell disease or steno-occlusive cerebral arteriopathies. In 2005, Wraige et al.[7] suggested a modified paediatric classification; this was implemented retrospectively at two tertiary paediatric neurology centres in London, UK, and has been known since as the 'classification of Ganesan'. The primary aim of our population-based study was to assess neuroimaging characteristics according to the location of the ischaemic lesion and vascular distribution area in relation to the timing and mode of imaging. The secondary aim was to evaluate the implementation of the Ganesan classification in a Swiss cohort and also to compare the participants in the original study[7] with our children with AIS.

METHOD

A total of 94 children with AIS were registered prospectively by the population-based Swiss Neuropaediatric Stroke Registry from 2000 to 2006.[8] Participants were aged 1 month to 16 years with a focal neurological deficit of acute onset, and computerized tomography (CT) or magnetic resonance imaging (MRI) findings showing infarction in a localization consistent with the neurological signs and symptoms.

All available neuroimaging findings obtained in the acute phase (<14d after stroke) and at follow-up were collected for

review. Neuroimaging studies were performed at different centres involved in the care of the children (hospitals in Berne, Zurich, Aarau, Neuchâtel, Geneva, Basle, Chur, Bellinzona, Lausanne, Lucerne, Sion, and St. Gallen) according to their local protocols. Review was performed blinded by a neuroradiologist (LR) and a neuropaediatrician (EB).

During the acute phase (<14d after stroke), if diffusion-weighted imaging (DWI) and T2-weighted MRI sequences were not available, CT was performed. In several participants, time-of-flight MRI or contrast magnetic resonance angiography (cMRA) was performed in addition to MRI. Time-of-flight MRA was the most frequently used modality because it avoids the repeated administration of contrast and is sufficiently reliable to detect arteriopathies.[9] cMRA, although of even higher quality and accuracy than time-of-flight MRA, was performed less often. Thus, to simplify matters, if MRA was performed it is called MRA, irrespective of the exact method. The following anatomical locations were examined for the site involved: right and left frontal, parietal, temporal, and occipital lobes; basal ganglia with caudate nucleus, putamen, pallidum, and internal capsule; insula and claustrum, thalamus, brainstem, cerebellar peduncles, and cerebellum. Subcortical infarction was defined as ischaemic involvement of the basal ganglia and/or thalamus and cortical infarction as ischaemic involvement of the white matter and/or cortex. Secondary changes such as peri-infarct oedema or sulcal enlargement were not considered important for this categorization. The distribution of vascular involvement of the internal carotid artery, middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery and their segments, the anterior choroidal and thalamoperforating arteries, the inferior, middle, and superior parts of the basilar artery, and the superior and inferior cerebellar arteries was analysed. Follow-up imaging studies (>14d after stroke) were evaluated for changes in lesion size compared with the initial image (especially with the size of lesion on DWI), atrophy, and possible normalization of abnormalities. MRA studies were analysed with respect to the localization (as above for vascular distribution), and the arterial abnormalities were classified as stenosis, occlusion, irregularity, arterial dissection, and luxury perfusion.

The additional data important for the paediatric stroke classification proposed by Wraige et al.[7] were collected by case note review of the data set of the Swiss Neuropaediatric Stroke Registry.[8] The categorization was carried out by the first author based on available vignettes comprising a brief synopsis of the clinical presentation and summarized laboratory results. Registration methods and data from this registry on incidence, manifestation, risk factors, and short-term neurological outcome were published by Steinlin et al.[8] The categories of the original paediatric stroke classification were as follows: (1) sickle cell disease; (2) cardioembolic disease; (3) moyamoya disease/syndrome; (4) cervical arterial dissection; (5) stenoocclusive cerebral arteriopathy; (6) other determined aetiology including specific cerebral arteriopathies not classified in subtypes 3–5; (7) multiple probable/possible aetiologies such as fibromuscular dysplasia or prothrombotic disorder; and (8) undetermined aetiology. The categories are a mixture of aetiology, syndrome, and pathology and represent a pragmatic approach. Criteria applicable to all subtypes are brain imaging findings consistent with AIS and, if present, cerebral arterial abnormalities in the territory of affected vessels.[7]

What this study adds

- This is the first population-based evaluation of neuroimaging in children with AIS.
- Our findings revealed that the anterior circulation territory is most frequently affected and that ACA involvement occurs only in conjunction with MCA lesions.
- The paediatric stroke classification of Ganesan was applied to our participants and appeared to be a reasonable tool.
- The results show a poor correlation between lesion pattern and aetiology.

The Swiss Neuropaediatric Stroke Registry is approved by the local ethics committee of the University Hospital in Berne, Switzerland, and has special approval from the Swiss National Ministry of Health for collecting epidemiological data.

RESULTS

Of 94 children with AIS, neuroimaging findings were available for 79 children (48 males, 31 females; median age at stroke was 5y 3mo, range 2mo–15y 8mo); for technical reasons, the neuroimaging findings of the other 15 children could not be adequately re-evaluated. Images from the acute period available for review comprised CT images in 41 children (in 22 children obtained during day 1, i.e. within the first 24h, and in five children during day 2) and magnetic MRIs in 57 (17 during day 1 and 16 during day 2); in 26 children, both CT and MRI were performed. MRA images were available for 42 children. Follow-up neuroimaging findings were available in 39 children (median time 4.3mo, range 15d–27mo 24d): CT was carried out in one child, MRI in 38, and MRA in 26 children. In five children, MRI findings were available only for the follow-up period (median time 6mo 12d; range 1mo–56mo 24d).

Timing and mode of imaging

The results of our cohort are summarized in Table I.

Table I: Modality, timing, and results of neuroimaging in 79 children with arterial ischaemic stroke

Modality	Results	Day 1	Day 2	Day 3	Day 4–14	Day >14
CT	Normal	3	0	0	2	0
	Abnormal	19	5	3	9	1
MRI	T2W normal, DWI abnormal	2	2	0	0	0
	T2W abnormal, DWI not performed	2	2	1	4	34
	T2W and DWI abnormal	13	12	4	15	4
MRA	Normal	4	2	1	3	8
	Arterial abnormalities	9	9	3	11	18

CT, computed tomography; MRI, magnetic resonance imaging; T2W, T2-weighted imaging; DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography.

Initial normal CT

In four children, CT images were normal (in three cases CT was performed within the first 12h). Two of these children showed small lesions in the vascular territory of the MCA; the findings of MRI, performed at 7 hours in one child and at 24 hours in the other, were pathological. The two other children had small lesions in the posterior circulation territory. One small lesion in the territory supplied by the posterior inferior cerebellar artery in the medulla oblongata was visible only on DWIs. In the other child, it was most likely that a stenosis in the P2 segment visible in MRA led to a lesion in the occipital lobe, subsequently visible on MRI.

Diffusion-weighted imaging

If performed, DWI in the acute period (n=48) was diagnostic in all cases, but T2-weighted MRIs were normal in four participants, all of whom had very small lesions involving the anterior as well as the posterior circulation territory and consistent with the clinical findings. In all 18 children in whom DWI was performed in the acute phase, and in whom follow-up imaging findings were also available, the size of the initial lesion was similar to the size of the lesion on follow-up imaging. In four participants, follow-up DWI revealed diffusion restriction after 2–4 weeks. In these four children, either the area of pathology apparent on DWI had increased compared with the initial imaging or new ischaemic lesions were detected.

Arterial abnormalities

MRA of the circle of Willis and intracranial arteries (n=42) in the acute period was normal in only 10 participants. MRA was used to image cervical vessels in only 11 children, two of whom had an arterial dissection. Intracranial abnormalities were identified in 32 children, affecting the MCA 33 times. Figure 1 summarizes the anatomical distribution of the intracranial arterial abnormalities of the whole group. In several children, more than one vessel was involved. Stenosis was present in 12 arteries, there was complete occlusion in 14 arteries, and in four cases there were irregularities in the lumen of the arteries. In four MRAs, there were signs of luxury perfusion, in three of them combined with stenosis. Follow-up imaging (>14d after stroke) was available in 26 participants, in 22 of whom MRA findings were available from both the acute phase and follow-up after 4 days to 7 months. A total of 14 participants showed persistent findings in the follow-up examination. Three participants had partial and five showed complete recanalization, the earliest detected within 4 days after the stroke. This recanalization was detectable on MRA performed after a mean interval of 3.5 months (range 4d–6.5mo) following the acute event.

Localization

A summary of the localization of infarction in relation to vascular territory is given in Table II. Right-sided infarction was present in 36 children, left-sided in 37, and bilateral in 14 children. The involved area was the anterior circulation territory in 55 children, the posterior circulation territory in 16, and both in eight children. Involvement of the ACA was never seen in isolation and occurred only in combination with an MCA lesion. However, out of 63 participants with infarction in anterior circulation territory (anterior and middle cerebral artery), the lesion was cortical in 25, cortical–subcortical with involvement of the basal ganglia in 30, and subcortical with involvement of the basal ganglia alone in eight participants. Infarction within the posterior circulation territory (posterior cerebral artery and basilar artery) included cortical infarction in 13, concurrent thalamus infarction in eight, and an isolated thalamic lesion in only three children. In eight participants both the anterior and posterior circulation were involved. Involvement of the unilateral anterior circulation alone was present in 60% and of the posterior circulation alone in 17% of participants; bilateral infarction, anterior and/or posterior, was present in 23% of participants.

The estimated volume in the areas of the cerebral arteries was very variable, in both the posterior and anterior circulation territory.

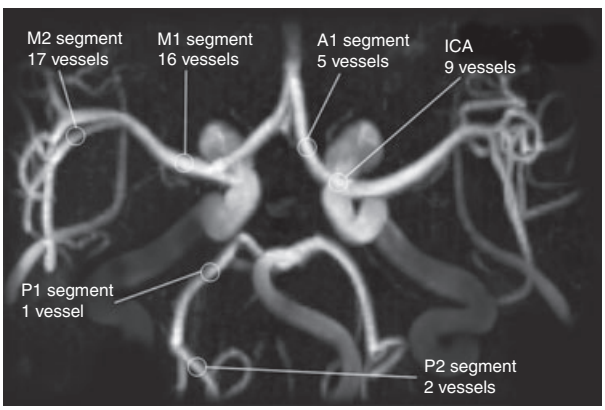

Figure 1: Magnetic resonance angiogram (summary of data from the whole group in acute imaging) with schematic representation of the number of affected vessels at each site. ICA, internal carotid artery.

Table II: Vascular territory involved in 79 children with arterial ischaemic stroke

		Unilateral[a]	Bilateral
Anterior circulation (n=55)	Cortical/subcortical	19	3
	Cortical/subcortical and basal ganglia	21	4
	Basal ganglia	8	0
Posterior circulation (n=16)	Cortical/subcortical	6	3
	Cortical/subcortical and thalamus	4	0
	Thalamus	3	0
Anterior and posterior (n=8)		4	4

[a]Right side anterior, 25/55; left side anterior, 23/55; right side posterior, 6/16; left side posterior, 7/16.

Table III: Paediatric stroke classification in our Swiss cohort compared with that of Wraige et al.[7]

Subtype of paediatric stroke classification, *n* (%)	Swiss cohort (*n*=79)	Wraige et al. (*n*=135)
Sickle cell disease	0	16 (12)
Cardioembolic	16 (20)	10 (7)
Moyamoya disease/syndrome	5 (6)	18 (13)
Arterial dissection	2 (3)	12 (9)
Steno-occlusive cerebral arteriopathy	25 (31)	42 (31)
Other determined aetiology	16 (20)	15 (11)
Multiple probable/possible aetiologies	8 (10)	7 (5)
Undetermined aetiology	4 (5)	15 (11)
Not classifiable[a]	3 (5)	0

[a]Not classifiable because of lack of clinical and radiological information (e.g. no magnetic resonance angiography).

Classification according to Ganesan

As summarized in Table III, paediatric stroke classification subtypes according to the Ganesan classification could be identified in 76 of our 79 children; three were not classifiable because of lack of information. Under the definition of subtype 3, children were included with neuroradiological findings attributable to moyamoya disease and moyamoya syndrome.

The radiological findings in association with paediatric stroke classification are summarized in Table IV. As previously mentioned, in our cohort, an ischaemic lesion in the area of the ACA was always seen in combination with a MCA lesion. Thus, to simplify matters in this summary, we use MCA as a synonym for anterior circulation territory. It is noteworthy that cortical–subcortical MCA lesions were the most common (21/25) in subtype 5, steno-occlusive arteriopathy. Multiple sites were most likely (6/16) to be affected in subtype 2, 'cardioembolic'. A total of 16 out of 79 children could be classified as subtype 6, 'other determined aetiology,' with the probable diagnosis stated as vasculitis and/or infection (6/2), minor trauma (2), and migrainous infarction (2)[10] according to the international headache classification (ICDH-II).[11] Although children with subtype 7 had variable main risk factors (leukaemia, minimal head trauma, renal failure, etc.), it is of interest that 5 out of 8 children had stroke related to an infection, usually viral infection of the respiratory tract.

DISCUSSION

Neuroimaging is of great importance in the diagnosis of childhood AIS, and has a major influence on its acute and long-term management. Our finding that the most commonly involved artery is the MCA (55/79, 70%) confirms reports in the literature.[12,13] In addition, and confirming the findings of Miravet et al.,[4] involvement of the ACA was never seen in isolation and occurred only in combination with an MCA lesion. Whether this is a constant finding in paediatric AIS should be confirmed in a larger cohort. Approximately half of strokes in our cohort were due to small vessel lesions, i.e. of the lenticulostriate or thalamoperforating arteries, with isolated involvement of the basal ganglia and thalamus respectively, and about half were attributable to lesions involving the MCA or posterior cerebral artery with cortical involvement. The fact that arteriopathies of small vessels such as the lenticulostriate or thalamoperforating arteries are more common in children than in adults might affect the frequency with which thrombolysis is indicated.[14,15] In adults, a diagnosis of isolated lacunar infarction in the acute stage has currently unresolved implications for management and has been less well characterized than other subtypes of stroke.[16]

Initial CT was normal in four children, confirming the well-known fact that CT in the early hours after stroke does not reliably exclude an ischaemic lesion. This must be considered particularly in individuals with small lesions in the posterior circulation territory, as described in two of our participants with similar findings of a cerebellar lesion and minimal ischaemia of the medulla oblongata. These findings indicate that MRI with DWI is the criterion standard in the diagnosis of an ischaemic lesion, whereas T2-weighted MRI can appear normal within the first 2 days, as observed in four children. Further, the method is sensitive enough to detect lesions in follow-up examinations. In some of our participants, within 4 weeks either an augmentation of infarction territory was found or new clinically silent lesions were detected. Whether this worsening of the findings might be prevented in the future by more aggressive treatment, such as intravenous lysis, requires further study.

Acute MRA showed a vasculopathy in 78% of participants, which is consistent with findings in the literature.[17,18] This is

Table IV: Radiological pattern compared with paediatric stroke classification

		Unilateral anterior			Unilateral posterior			
Paediatric stroke classification	*n*	MCA[a]	MCA and BG	BG	PCA	PCA and thalamus	Thalamus	Multiple sites
Sickle cell disease	0	0	0	0	0	0	0	0
Cardioembolic	16	6	2	1	0	1	0	6
Moyamoya disease/syndrome	5	2	1	0	0	0	0	2
Arterial dissection	2	1	1	0	0	0	0	0
Steno-occlusive cerebral arteriopathy	25	5	16	0	2	0	0	2
Other determined aetiology	16	5	0	3	1	3	0	4
Multiple probable/possible aetiologies	8	0	1	1	1	1	2	2
Undetermined aetiology	4	0	0	2	0	0	1	1
Not classifiable	3	0	1	0	1	0	0	1

[a]Anterior cerebral artery involvement was never seen in isolation without involvement of middle cerebral artery (MCA) territory. PCA, posterior cerebral artery; BG, basal ganglia.

important information, as Fullerton et al.[18] and Ganesan et al.[19] demonstrated that vasculopathy is one of the major risk factors for recurrence. Thus, the presence of vasculopathy is likely to influence the prescription of prophylactic treatment with platelet inhibitors, in view of the lack of evidence-based data on the effect of prophylactic treatment. The above contribution to management in the presence of vasculopathy and the fact that MRA might already normalize within the first few days (4d in the case of our participant) stresses the importance of vascular imaging, preferably with MRA, in the initial investigation of the children.

The Ganesan classification is population based, and so it is also appropriate for our Swiss cohort. Differences between the ethnic populations and recruitment hospitals (tertiary versus community based) have to be considered. However, the pattern of MRI and the findings on MRA alone do not provide enough information for aetiological attribution. Findings such as frequent multiple lesions in children with cardiac problems and larger territory infarctions in those with stenosing vasculopathies might be helpful, but are not exclusive. The lack of participants with sickle cell disease is explicable on ethnic grounds, and the relatively less frequent occurrence of arterial dissection may be a result of the lack of cervical MRA, which was often not performed. As reported recently elsewhere,[20] our study shows that arterial ischaemic stroke in children is most often associated with a combination of predisposing conditions. This might also be why it is difficult to have an investigative protocol on the basis of neuroimaging findings. The only hint given by our data is that, in the case of MCA and basal ganglia involvement, a steno-occlusive cerebral arteriopathy has to be searched for.

Despite the notable number of participants included, the value of our results may be limited by the fact that they were investigated and treated in 12 different hospitals according to their local protocols. For instance, not every child underwent an MRI, intracranial MRA, or cervical MRA. Perfusion CT was not used at all. Therefore, and because of the varying timings, comparability is restricted. Concerning the proposed application of Ganesan's classification, it must be borne in mind that our participant cohorts were recruited in various hospitals (tertiary and community based), and the differences between the ethnic backgrounds must be taken into account.

CONCLUSION

DWI was the most reliable method of detecting lesions during the acute phase. T2-weighted MRI and CT can be normal within the first 2 days. MRA in the acute period revealed abnormalities in 78%, but recanalization in 8 out of 22 children (36%). Thus, MRI including DWI and MRA are the best and most important investigations in children with suspected AIS.

The incidence of involvement of cortical structures and/or white matter was about the same, whether or not basal ganglia or thalamus lesions respectively, were present; however, isolated basal ganglia–thalamus involvement was markedly less frequent. Although conclusive in some subtypes of AIS, neuroimaging patterns such as arterial dissection or moyamoya may guide our search for risk factors, but the pattern alone cannot ascertain them.

REFERENCES

1. Amlie-Lefond C, Sebire G, Fullerton HJ. Recent developments in childhood arterial ischaemic stroke. *Lancet Neurol* 2008; **7:** 425–35.
2. Fullerton HJ, Johnston SC, Smith WS. Arterial dissection and stroke in children. *Neurology* 2001; **57:** 1155–60.
3. Buompadre MC, Arroyo HA. Basal ganglia and internal capsule stroke in childhood – risk factors, neuroimaging, and outcome in a series of 28 patients: a tertiary hospital experience. *J Child Neurol* 2009; **24:** 685–91.
4. Miravet E, Danchaivijitr N, Basu H, Saunders DE, Ganesan V. Clinical and radiological features of childhood cerebral infarction following varicella zoster virus infection. *Dev Med Child Neurol* 2007; **49:** 417–22.
5. Braun KP, Kappelle LJ, Kirkham FJ, Deveber G. Diagnostic pitfalls in paediatric ischaemic stroke. *Dev Med Child Neurol* 2006; **48:** 985–90.
6. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol* 2005; **58:** 688–97.
7. Wraige E, Pohl KR, Ganesan V. A proposed classification for subtypes of arterial ischaemic stroke in children. *Dev Med Child Neurol* 2005; **47:** 252–6.
8. Steinlin M, Pfister I, Pavlovic J, et al. The first three years of the Swiss Neuropaediatric Stroke Registry (SNPSR): a population-based study of incidence, symptoms and risk factors. *Neuropediatrics* 2005; **36:** 90–7.
9. Muir KW, Buchan A, von Kummer R, Rother J, Baron JC. Imaging of acute stroke. *Lancet Neurol* 2006; **5:** 755–68.
10. Ebinger F, Boor R, Gawehn J, Reitter B. Ischemic stroke and migraine in childhood: coincidence or causal relation? *J Child Neurol* 1999; **14:** 451–5.
11. Sancisi E, Cevoli S, Pierangeli G, et al. Application of ICHD-II and revised diagnostic criteria to patients with chronic daily headache. *Neurol Sci* 2007; **28:** 2–8.
12. Delsing BJ, Catsman-Berrevoets CE, Appel IM. Early prognostic indicators of outcome in ischemic childhood stroke. *Pediatr Neurol* 2001; **24:** 283–9.
13. Matta AP, Galvao KR, Oliveira BS. Cerebrovascular disorders in childhood: etiology, clinical presentation, and neuroimaging findings in a case series study. *Arq Neuropsiquiatr* 2006; **64:** 181–5.
14. Amlie-Lefond C, Chan AK, Kirton A, et al. Thrombolysis in acute childhood stroke: design and challenges of the thrombolysis in pediatric stroke clinical trial. *Neuroepidemiology* 2009; **32:** 279–86.
15. Ganesan V. Thrombolysis in paediatric arterial ischaemic stroke. *Dev Med Child Neurol* 2009; **51:** 90–1.
16. Norrving B. Long-term prognosis after lacunar infarction. *Lancet Neurol* 2003; **2:** 238–45.
17. Danchaivijitr N, Cox TC, Saunders DE, Ganesan V. Evolution of cerebral arteriopathies in childhood arterial ischemic stroke. *Ann Neurol* 2006; **59:** 620–6.
18. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. *Pediatrics* 2007; **119:** 495–501.
19. Ganesan V, Prengler M, Wade A, Kirkham FJ. Clinical and radiological recurrence after childhood arterial ischemic stroke. *Circulation* 2006; **114:** 2170–7.
20. Del Balzo F, Spalice A, Ruggieri M, Greco F, Properzi E, Iannetti P. Stroke in children: inherited and acquired factors and age-related variations in the presentation of 48 paediatric patients. *Acta Paediatr* 2009; **98:** 1130–6.