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# THE CORRELATION BETWEEN MAGNETIC RESONANCE ANGIOGRAPHY FINDINGS AND THE AETIOLOGY OF CHILDHOOD ARTERIAL ISCHEMIC STROKE

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Received: January 23, 2014 Accepted: Mart 3, 2014 Objective - To describe the magnetic resonance imaging (MRI) and time-of-flight (TOF)-magnetic resonance angiography (MRA) characteristics of children with arterial ischemic stroke and correlate them with the aetiology. Methods - We performed a retrospective review of clinical records and imaging (MRI and MRA) of 34 children (8 months to 17 years) with arterial ischemic stroke. Results - The group contained 14 females and 20 males. Risk factors were congenital heart disease (CHD) in 8, sickle cell disease in 2, prothrombotic abnormalities in 7, vasculitis in 5 (varicella in 2, neuroborreliosis in 1), trauma in 3, steno-occlusive cerebral arteriopathy, herniation due to intracranial bleeding, complication of aneurysmal subarachnoid haemorrhage with vasospasm, and arterial dissection with and without previous trauma. In 5 of the 34 patients the aetiology was undetermined. The most common infarctions were observed in the distribution of the middle cerebral artery, followed by the posterior circulation. The intracranial MRA was normal in 15 of the 34 children. In all but one patient with cryptogenic stroke MRA was normal. Conclusion – MRI is helpful to determine the exact location and limit of the infarct zone. The absence of cerebral arteriopathy on TOF-MRA in childhood stroke suggests a nonvascular cause; mainly cryptogenic stroke, but also prothrombotic abnormalities and CHD.

Key words: Children • MRI • MRA • Stroke.

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#### Introduction

Stroke in children has a different aetiology and outcome than that of the adult population. It is still uncommon (approximately 2-6/100,000 children) (1) but is not an exceptional event during childhood. Up to 25% of the children, who have already suffered one stroke, will have a new ischemia (1). Unfortunately, there is a lack of awareness regarding cerebral vascular disease in paediatricians. Clinical presentation varies according to age and the vascular territory involved. Magnetic resonance imaging (MRI) is the method of choice in paediatric stroke. It not only diagnoses the arterial ischemic event, but is also able to rule out causes of pseudo strokes, such as infections, demyelination, neoplasm, drug related symptoms, phacomatosis, and miscellaneous disorders. Diffusion-weighted imaging (DWI) plays the main role in the diagnosis of paediatric cerebral infarction (see Fig. 1). In addition, MRI is able to forecast later development, i.e. diffusion tensor imagingbased tractography at 3 months can be used to predict neurodevelopment outcome after perinatal arterial ischemic stroke (2, 3). According to the international paediatric stroke group, magnetic resonance angiography (MRA) plays an important role in ruling out abnormalities of the intracranial and cervical circulation and can to a certain extend predict the prognosis (4).

The purpose of this retrospective study is to answer the following questions: (a) Which pathological conditions are found more often? (b) How often do children with stroke have MRA abnormalities? (c) Is there a difference between the groups of patients with normal and pathological MRA? (d) Can we suggest probable aetiologies based on MRA findings?

## Material and methods

## Subjects

Clinical histories and discharge diagnosis were obtained from written records, including discharge summaries. All patients underwent MRI and MRA. 34 children with arterial ischemic infarcts were included during a five year period. All but one child presented with stroke for the first time. No perinatal strokes were included. Informed consent was obtained from the parents or from the respective guardians for each imaging study.

## Imaging studies

During a period of 5 years, 34 children with arterial brain ischemic infarcts were examined using a 3-T unit (Verio, Siemens, Erlangen, Germany).

Our standard protocol for stroke evaluation includes axial T2, T2\*, fluid-attenuated inversion recovery (FLAIR) and DWI, together with maps of calculated apparent diffusion coefficients. In addition, a 3-dimensional time-of-flight (TOF) magnetic resonance angiography (field of view: 199 mm) was performed of the circle of Willis, with secondary maximum intensity projection (MIP) reconstruction. The field of view encompassed the anterior branches of the middle cerebral artery up to the M3 segment. The use of sequences with thin slices (0.5 mm) and a 385 matrix to decrease voxels, combined with an analysis of the raw image, permits differentiation between an artefact and a vascular lesion. TOF MRA was performed within 48 hours of arrival in the clinic in all children, and mostly within 24 hours. In cases of suspected dissection, a cervicocerebral axial T1-weighted image with fat suppression and contrast-enhanced MRA were added.

## Image evaluation

Image evaluation was performed separately and independently by two experienced radiologists on standard post-processing Picture Archiving and Communication system (PACS) workstations (Centricity RIS 4.0i, GE Healthcare, USA) to avoid differences in the interpretations of images. The 'percentage interobserver agreement' was defined as the percentage interobserver agreement for DWI changes and MRA changes.

# Results

# Pathological conditions

Thirty-four patients had a complete clinical and radiological work-up and were eligible for inclusion in this study. Fourteen were female and 20 male, with ages ranging from 8 months to 17 years (median age of 6 years). Two patients had known sickle cell disease and 8 congenital heart diseases. Other risk factors were present: prothrombotic abnormalities in 7, vasculitis in 5 (prior *Varicella* in 2, neuroborreliosis in 1), trauma in 3, stenoocclusive cerebral arteriopathy, herniation due to intracranial bleeding, complication of subarachnoid haemorrhage with vasospasm, and arterial dissection without previous trauma. Only 5 of the 34 patients were cryptogenic.

#### MRA findings in children

The intracranial MRA was normal in 15 of the 34 children. The MRA-abnormalities found in 19 children were not only seen in the anterior circulation (n=14), as approximately one-sixth of the patients (3 out of 19) had abnormalities only in the posterior circulation. MRA abnormalities in the carotid and vertebrobasilar system were present in 1 patient. The MRA abnormalities were most common on the internal carotid artery (ICA) extending to the A1 segment of the anterior cerebral artery and/or the M1 segment (n=8), followed by middle cerebral artery (MCA) circulation (n=6), the vertebral artery (n=2), and the posterior cerebral artery (n=1). One patient showed multiple supra aortal stenosis extending to the ICA and vertebral artery. Another patient presented with agenesis of the right ICA and vertebral artery with the absence of the bony carotid canal on computed tomography. There was no stenosis.

When present, the MRA abnormalities correlated with area of infarct. The most common infarctions observed were in the distribution of the MCA, followed by those observed in the posterior circulation. Both distributions were present in 2 children. One patient showed a typical watershed infarction. No patient had isolated infarction in the distribution of the anterior cerebral artery (ACA) circulation, but 4 children presented with simultaneous infarctions within the distribution of ACA and MCA circulations.

Only one out of 5 patients with so called cryptogenic infarct showed a pathological MRA. The intracranial MRA was normal in 15 out of 34 patients. This group of patients with "normal" MRA also presented with risk factors of prothrombotic abnormalities in 7, and congenital heart disease in 4. Associated arteriopathy was present in 18 patients (1 patient showed no stenosis but did present with a vascular malformation). The most common site of arteriopathy was in the large intracranial arteries, in particular the proximal MCA and the distal ICA.

#### Interobserver agreement

Agreement was 89% for interobserver cerebrovascular imaging, i.e. MRA and 100% for interobserver DWI changes.

#### Discussion

# Childhood arterial ischemic stroke and pathological conditions

Male predominance, as in our study (59% were males), has been previously reported (5). In 23.5% of the children, ischemic stroke was related to cardiac disease. This result is in agreement with an extensive review of the literature with data on 391 children (6) in which the most frequently identified aetiology for arterial ischemic stroke in children was cardiac embolism (13.2%).

It is known that 11% of patients with sickle cell disease (SCD) will have a clinical or subclinical stroke before 20 years of age (1). In our patients with SCD, TOF MRA showed no involvement of the posterior circulation. This is in agreement with the literature (1) which describes a relative sparing of the area.

Another common predisposing factor was the existence of prothrombotic abnormalities. Lanthier et al. (6) showed that these are, aetiologically, particularly important in combination with other risk factors. Prothrombotic disorder should be considered *only* a risk factor; therefore other aetiologies should be ruled out.

Unlike adults, children with arterial dissection usually present with an acute stroke (1). In 3 (all boys) out of 34 children, stroke was caused by arterial dissection, which is probably an under-diagnosed cause. The aetiology of arterial dissection appears to be either trauma (2 out of 3 patients) or cryptogenic (1 out of 3 patients). Craniocervical arterial dissection should be included in the differential diagnosis, especially in boys with posterior circulation involvement (7). In addition, evidence is accumulating that children with posterior circulation infarction have a high frequency of arterial disease, particularly dissection of the vertebral arteries. Ganesan et al. (8) reported that cervical arterial abnormalities are relatively common in children with ischemic infarction, in particular if the posterior circulation was involved. In the same study, Ganesan et al. (8) also described the simultaneous presence of abnormalities of the intracranial and cervical arteries and suggested that the data published up to now have probably underestimated cervical arteriopathy in childhood stroke. In addition, infection and inflammation have often been recognized as an activate factor for arteriopathy and secondary childhood stroke (9). In 5 patients, stroke was caused by vasculitis. Of these, one stroke was due to Lyme neuroborreliosis and two following a Varicella zoster infection.

## MRA findings in children

Neuroimaging, and specifically MRI, plays a central role in the diagnosis of childhood stroke. The main drawback to performing MRI in children is the sensitivity to motion. Classically, a clear advantage of TOF MRA is to obtain high-quality images in multiple projections without contrast and the exclusion of vessel overlap. It is an unenhanced technique based on blood flow-related signal variations, which at the same time suppresses the signal of the stationary tissue. In case of childhood stroke, the combination of MRI and TOF MRA has proven ideal because anatomical sequences can be performed in juxtaposition to the angiographic evaluation. This permits the correlation of the vascular territory to the affected parenchymal area on DWI and ADC maps (Fig. 1). TOF MRA usually reveals a scarcity of vessels within the infarcted brain, with narrowing or occlusion of the supplying vessels (Fig. 2).

More than half of the children (53%) with childhood stroke presented with arteriopathy (the patient with agenesis but no stenosis, was not included). This percentage is in agreement with previous publications (1, 10) which report nonatherosclerotic craniocervical arteriopathy in 50% to 80% of children with stroke. According to Husson et al. (11) there is a very good correlation between TOF MRA and conventional contrast angiography for the detection of intracerebral arterial lesions in childhood stroke.

In most cases, children presented with nonatheromatous changes of the cranicervical circulation. With the exception of 2 patients (one with multiple supra aortal stenosis and another with vascular malformation) the most common site of arteriopathy was in the large intracranial arteries, in particular the proximal MCA and the distal ICA (both locations corresponding to 79% of all cases of vascular changes seen in our sample of childhood stroke). This location has been repeatedly observed as the most common in paediatric stroke (11-13). Indeed, this site is so common that it led Sébire et al. (13) to propose the terminology "transient cerebral arteriopathy" (TCA). It is described as a unilateral focal and segmental stenosis involving the distal part of the terminal ICA and proximal MCA and anterior cerebral artery. This expression has been mostly associated with infarction involving the anterior circulation (Fig. 2).

In an excellent review, Braun et al. (14) evaluated the outcome of children with ischemic stroke and unilateral focal cerebral





A: DWI imaging reveals restricted diffusion, compatible with an acute infarct in the right MCA territory. B: Severe ADC decrease in the right MCA territory, well correlated with the neuronal injury detected on the DWI imaging.

C: Perfusion demonstrates a wide hypoperfused area ["time-to-peak" (TTP) delays of about 5 seconds]. The difference between the ADC and TTP maps corresponds to the mismatch right frontal area that represents tissue at risk of infarction if early reperfusion is not obtained. The diffusion–perfusion mismatch area might possibly correspond to the so-called ischemic penumbra, i.e. the hypoperfused brain parenchyma with potentially reversible altered cell metabolism.

D: TOF MRA of the circle of Willis reveals irregularity with partial occlusion of one of the M2 branches of the right MCA (see white arrow).

arteriopathy (FCA) of childhood. Approximately 25% of the children showed complete regression of the focal stenoses at an 18-month follow-up, and in 20% there was a partial deterioration before improvement. Clear progression of the vasculopathy was seen in only 6% of patients. Some authors (15) support the hypothesis that FCA is a consequence of an infection; i.e. it probably results from an inflammatory response to infections such as varicella, Borrelia or tonsillitis. The problem is that the literature can be confusing, but in reality all these terminologies [including TCA, large-vessel childhood primary angitiis of the central nervous system (CNS) and FCA] probably refer to the same pathological entity (16) with inflammation being the underlying pathomechanism (17).

MRI is not specific enough to separate primary and secondary vasculitis; although the first is usually focal and the second more diffuse. In addition, non-progressive primary



**Fig. 2** *MR images of a 9-year-old boy with acute ischemic infarction. A, B within 4 hours after clinical presentation and C, D after 24 hours.* 

A: DWI imaging shows restricted diffusion, compatible with an acute right MCA territory infarct.

B: TOF MRA of the circle of Willis reveals irregular stenoses and "beading" with partial occlusion of the M1 segment of the right MCA.

C/D: After 24 hours increased restricted diffusion, i.e. infarcted brain tissue on DWI imaging with recanalization, i.e. stenosis regression on MRA after heparin therapy.

angitiis of the CNS has a monophasic character (18). If the inflammatory vascular changes are restricted to the brain and spinal cord it is called primary CNS vasculitis. A further diagnostic evaluation is necessary in the case of secondary CNS vasculitis (17).

# MRA findings and probable etiologies

In our review, a "normal" MRA was only found in patients with cryptogenic stroke, prothrombotic abnormalities and congenital heart disease. Our results are in agreement with Munot et al., (12) who reported that children with childhood stroke and "normal" MRA, i.e. without cerebral arteriopathy, have nonvascular risk factors. In contrast, it is known (8) that abnormal MRA is related with a higher risk of recurrence. According, the only patient in our series who presented with two episodes of infarct had a clear abnormality on MRA with multiple supra aortal stenosis.

# Limitations

The relatively small number of patients that could be included in this study was a significant limitation. A second limitation was that our patients were only evaluated with TOF MRA, rather than with doppler sonography or catheter angiography. Another limitation of the TOF MRA was the size of the field of view. It is possible with TOF MRA that small cranial arteriopathy could have been missed, for example arterial occlusions beyond M3 segment of the middle cerebral artery.

## Conclusion

MRI and MRA are useful for visualising the location and suggesting the aetiology of the infarction. Not only pathological findings of MRA such as arteriopathy, but also normal MRA are also helpful for suggesting prothrombotic abnormalities, congenital heart disease, and cryptogenic infarction in paediatric age.

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**Conflict of interest:** The authors declare that they have no conflict of interest.

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