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Short communication

Incidence and diagnosis of unilateral arterial cerebral infarction in newborn infants *

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Abstract

Aims: Magnetic resonance imaging (MRI) is accepted as the gold standard for the diagnosis of arterial cerebral infarction (ACI), but few studies have reported the incidence of neonatal ACI based on MRI findings. We provide new population-based epidemiologic and diagnostic data on all infants diagnosed between 1997 and 2002 in our center with an MRI-confirmed diagnosis of unilateral neonatal ACI.

Results: Nine patients were identified, giving an incidence of 1:2300 unilateral ACIs in our inborn population. In all patients the middle cerebral artery was affected. Seven patients showed epileptic seizures, usually starting within the first 3 days of life. EEG was pathologic in all patients. Only three infarctions were diagnosed by ultrasound. Initial MRI established diagnosis of ACI in eight out of nine patients and subsequent MRI described the exact location of infarctions in all patients. Six out of nine patients developed hemiparesis and five had deficits in language development. There is a substantial need for special care facilities and long-term therapeutic interventions.

Conclusions: The incidence of neonatal ACI is higher than previously reported. The sensitivity of early cerebral ultrasound for diagnosis of ACI is low. Seizures in the first 3 days of life combined with pathologic EEG findings should lead to MRI, regardless of normal cerebral ultrasound.

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Introduction

Symptomatic unilateral arterial cerebral infarction (ACI) in newborn infants usually occurs in the territory of a major cerebral artery, most often in the middle cerebral artery (MCA) [1], with a predominance of the left side [3]. The majority of infants do not suffer from asphyxia, but present with seizures during the very first days of life [7]. Cranial magnetic resonance imaging (MRI) is accepted as the gold standard for the diagnosis of ACI [8], while the diagnostic role of cerebral ultrasound is controversial [1, 4, 5]. Few studies have used MRI for diagnosis during the neonatal period [1, 8] and few population-based epidemiologic data exist. Most authors estimate an incidence of 1:4000 ACIs based on a study that used computed tomography (CT) and data from 1987–1993 [2, 10]. With neonatal MRI routinely available, we hypothesize that detection rates of ACI should be higher. The objective of this study was to provide current population-based epidemiologic data on the incidence of unilateral ACI in newborns and to elucidate the diagnostic value of newborn seizures, electroencephalography (EEG), cerebral ultrasound and MRI for the diagnosis of ACI.

Methods

Patients

All newborns born between 1/1/1997 and 12/31/2002 and diagnosed in the University Children's Hospital, Basel with a discharge diagnosis of MRI-proven unilateral ACI were identified using full-text searchable electronic databases of patient records and by hand-searching discharge letters from the Department of Neonatology and the Department of Pediatric Neurology.

Population

Our perinatal center consists of two major women's hospitals of the two Swiss cantons Basel-Stadt and Basel-Landschaft, with two associated tertiary-care neonatal units of the University Children's Hospital, Basel. The two

women's hospitals cover 50% of all deliveries in the two cantons and serve as both regional hospitals and referral centers. Inborn newborns were born in the two above-mentioned hospitals. In addition, there are four obstetric departments within the two provinces referring ill outborn children, and four hospitals in neighboring provinces that refer critically ill outborn children. Hospitals referring outborn children were free to choose our center for neonatal care or others from neighboring provinces. Therefore, to allow for a well-defined population, incidence was calculated for inborn children only, based on total birth rates from 1997 to 2002 in the two associated women's hospitals.

Evaluation of patient data

Information was obtained from obstetric and pediatric patient records. Patient charts, EEGs, cerebral ultrasounds, MRI images and data on neurodevelopmental follow-up were evaluated retrospectively.

Diagnostic procedures

All instrumental diagnostic procedures were performed during routine neonatal care. Initial EEGs with a minimum duration of 30 min and cerebral ultrasound studies were recorded in the neonatal intensive care unit (NICU) within 48 h after the onset of seizures. Ultrasound was carried out by consultant neonatologists and certified pediatric radiologists using Aloka SSD-1700 and Medison Digital Gaia ultrasound scanners with 5–7.5-MHz multifrequency sector transducers. MRI was carried out on a 1.0-T Picker system during the neonatal period in all but three patients (numbers 3, 4 and 7), who received their first MRI at the ages of 2, 3 and 8 months of life, respectively.

Results

Identified patients

From 11 patients with MRI-proven ACI, two were excluded because of multiple bilateral infarctions following severe asphyxia. Eight out of nine infants with unilateral ACI were identified during the neonatal period; one boy, who was without pathological findings as a neonate, was admitted to our center at the age of 4 months because of left-sided spasticity. Infants were born between 35 and 42 weeks of gestation. There were 13,901 inborn live births during the study period, and six of the nine identified patients were inborn. This translates to an incidence of 1:2316 unilateral neonatal ACIs. Characteristics and diagnostic details of all patients are shown in Table 1.

Diagnostic features

Seven out of nine patients showed neonatal seizures, and in six patients seizures started within the first 3 days of life. In four patients we observed focal clonic seizures, while three patients presented with generalized seizures consisting of apnea and generalized clonic and tonic convulsions. EEG recordings from all identified neonates were carried out within 48 h of the onset of seizures. All neonatal EEG recordings showed pathologic findings as follows: abnormal lateralized background (5), periodic lateralized epileptiform discharges (1), and focal hypersynchrony (7). In only three of eight patients did cerebral ultrasound show focal echogenic lesions suggesting ACI.

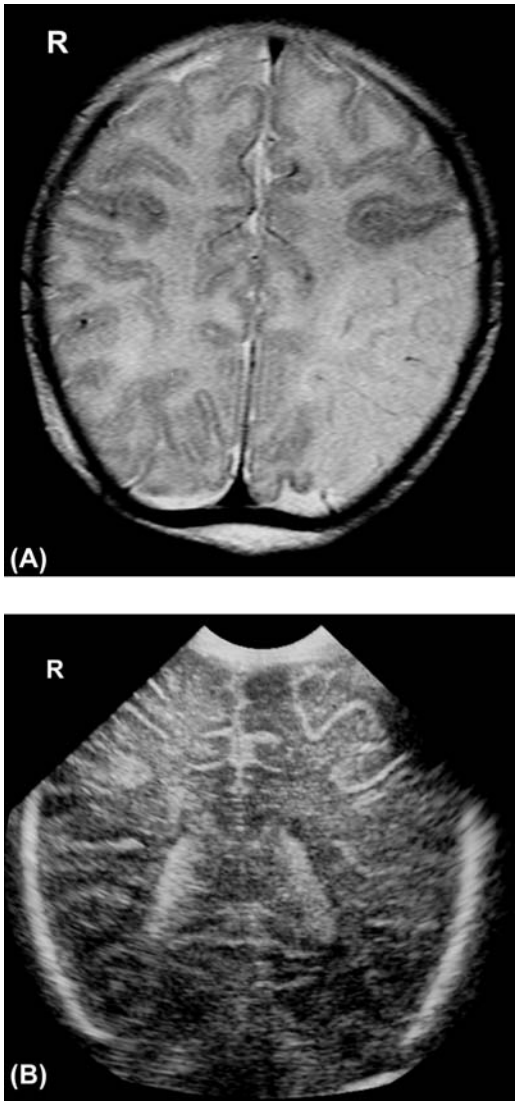

Figure 1 (A) Axial T1-weighted MRI (day 7) and (B) coronal cerebral ultrasound (day 5) of patient no. 8. MRI shows enhanced signal intensity of the left posterior hemisphere due to ischemic infarction of the left middle cerebral artery, while the cerebral ultrasound is unremarkable.

Table 1 Patient characteristics and diagnostic data of infants suffering from unilateral arterial cerebral infarction (n = 9)

No	Place of birth	GA	Sex	Pregnancy	CTG	Delivery	Apgar score (1′/5′)	Neurologic symptoms	Cerebral ultrasound	EEG	MRI	Affected regions
1	Inborn	35	M	Normal	N	Spontaneous, cervical Twisted cord	6/10	Day 1 focal clonic seizures left	Day 1 N	Day 1 background abnormal, focal hypersynchrony left	Day 3 infarction mca left	Hemisphere Basal ganglia Internal capsula
2	Inborn	41	M	Poly-hydramnion	N	Spontaneous, cervical Twisted cord	9/10	Day 1 generalized seizures	Day 2 echogenic lesion left	Day 3 background normal, focal hypersynchrony left	Day 11 parietooccipital bleeding left, infarction? vascular abnormality?	Hemisphere
3	Outborn	41	M	Normal	N	Spontaneous	9/6	Day 1 generalized seizures	Day 1, day 13 N	Day 12 background abnormal, focal hypersynchrony right	Week 9 infarction mca right	Hemisphere Basal ganglia Internal capsula
4	Inborn	41	F	Normal	P	Poor progress, vacuum	8/9	Day 1 generalized seizures	Day 1 N Day 2 echogenic lesion left	Day 2 background abnormal, PLEDs left	Day 11 infarction mca left	Hemisphere Basal ganglia
5	Inborn	36	F	Methadone, nicotine	N	Spontaneous, amniotic fluid meconium-stained	6/8	Opiate withdrawal syndrome, No seizures	Day 5 echogenic lesion left	Day 7 background normal, focal hypersynchrony left	Day 22 infarction mca left	Hemisphere Basal ganglia
6	Inborn	42	M	normal	N	Poor progress, vacuum	8/10	Day 2 focal clonic seizures right	Day 4 N	Day 3 background normal, focal hypersynchrony left	Week 14 infarction mca left	Hemisphere Basal ganglia
7	Outborn	40	F	Nicotine, placental infarcts	P	Emergency c/section	9/10	Neonatal period unremarkable, no neonatal diagnostic work-up 4 months: reduced motor movements left, beginning spasticity left 6 months: cerebral ultrasound porencephalic cyst right hemisphere 8 months: EEG normal			8 months infarction mca right	Hemisphere Basal ganglia Internal capsula
8	Inborn	41	F	Normal	N	Spontaneous	9/10	Day 3 focal clonic seizures right	Day 5, day 7 N	Day 4 background abnormal, focal hypersynchrony left, sharp/slow waves right	Day 7 infarction mca left	Hemisphere

(Table 1 continued)

No	Place of birth	GA	Sex	Pregnancy	CTG	Delivery	Apgar score (1′/5′)	Neurologic symptoms	Cerebral ultrasound	EEG	MRI	Affected regions
9	Outborn	39	F	Normal	N	Non-urgent c/section	9/10	Day 2 focal clonic seizures right	Day 2, day 3 N	Day 3 background abnormal, focal hypersynchrony left	Day 5 infarction mca left	Hemisphere

GA, gestational age; M, male; F, female; CTG, cardiotocogram; N, normal; P, pathologic; mca, middle cerebral artery; PLED, periodic lateralized epileptic discharges.

MRI confirmed the diagnosis of ACI in these three cases. Doppler studies were routinely carried out, but this was never helpful for the diagnosis of ACI.

Regarding MRI, a diagnosis of ACI was confirmed in eight out of nine cases after the first MRI scan. In one child, an initial MRI on day 11 showed considerable left-sided bleeding, suggesting hemorrhagic infarction of the left MCA, but bleeding due to a vascular malformation could not be ruled out. After resorption of the hematoma, subsequent MRI scans established the diagnosis of ACI. All patients had unilateral infarction of the middle cerebral artery (Figure 1). Seven out of nine infarctions were left-sided and two were right-sided. For details on the affected cerebral structures, see Table 1.

Neurological outcome

Six out of nine children developed hemiparesis, while two continued to show epileptic seizures after the neonatal period. Language development was delayed in five out of nine children. There is a substantial need for special care school facilities and long-term therapeutic interventions, as detailed in Table 2.

Discussion

The incidence of ca. 1:2300 unilateral neonatal ACIs in our population is higher than in another population-based study [2] in which an incidence of 1:4000 was calculated using cranial CT for confirmation of diagnosis. This discrepancy may be due to the fact that the sensitivity of MRI for diagnosis of ACI is superior to that of CT [6].

Newborn seizures were present in seven out of nine patients, a fact that underlines the value of this clinical condition for the diagnosis of ACI. As helpful as seizures are for initiation of the diagnostic and therapeutic process, two patients were without corresponding neurologic symptoms in the neonatal period. It remains unclear how these patients can be identified at an early date, because there are no predictive markers available. Furthermore, it is not known whether ACIs diagnosed acutely and retrospectively differ in the time of occurrence or pattern of injury [10].

All patients identified during the neonatal period had pathologic EEG recordings. Five out of eight EEG readings showed abnormal lateralizing background activity, indicating poor prognosis regarding the development of hemiparesis [8]. Only one patient showed periodic lateralized epileptiform discharges (PLEDs), known to be pathognomonic for unilateral ACI [9]. We may have missed PLEDs in other patients, as our EEG recordings lasted only 30–60 min, and were thus of a shorter duration than those reported in recent studies [8, 9], which used continuous EEG for nearly 2 days.

Table 2 Neurological and developmental outcome[a] of newborn infants suffering from unilateral arterial cerebral infarction (n = 9).

No	Motor Development	Epilepsy	Language development	Age-appropriate communication/ play behavior	School type	Current therapy/ support	Follow up (months)
1	Hemiparesis Arm > leg	+	Delayed	No	Special care	Physio Speech OT	72
2	Normal	–	Normal	Yes	Normal	–	48
3	Hemiparesis Leg > arm	–	Delayed	Yes	Normal	Physio Speech OT	48
4	Hemiparesis Arm > leg	–	Delayed	No	Special care	Physio SE, OT	60
5	Hemiparesis Leg > arm	–	Delayed	No	Special care	Physio SE	48
6	Hemiparesis	+	Delayed	No	Special care	Physio OT	42
7	Hemiparesis	–	Normal	Yes	–[b]	Physio OT	20
8	Normal	–	Normal	Yes	–[b]	Physio[c]	24
9	Normal	–	Normal	Yes	–[b]	Physio[c] SE	24

OT, occupational therapy; SE, special educative therapy.
[a]Based on Griffith's test (≤24 months of age) or Denver developmental scale (>24 months of age).
[b]Children are below 3 years of age.
[c]Prophylaxis.

We assume that the low sensitivity of cerebral ultrasound results from the timing of the initial ultrasound studies, as they were carried out in the first few days of life. There is evidence from prospective trials showing higher ultrasound sensitivity when carried out at the end of or after the first week of life [4, 8]. Cerebral Doppler studies were not helpful for the diagnosis of ACI in our patients. Some small series have identified transient decreases in cerebral blood-flow velocity ipsilateral to ACI in a proportion of affected infants [11, 12], while others did not [13]. One reason for this discrepancy could be that some infarctions might be caused by transient vasospasm rather than embolism. In addition, seizures are known to transiently increase blood flow velocity [14]. Furthermore, the inability to show reduced cerebral blood-flow velocities in our study might be due to the timing of the Doppler studies, which were carried out up to 48 h following the onset of seizures. Decreased blood-flow velocity in ACI seems to be significant only within the first 24 h [11]. In general, cerebral blood-flow velocity varies substantially following neonatal seizures due to ACI, and the usefulness of these measurements in ACI has not yet been established [10].

Conventional MRI proved to be very sensitive for the diagnosis of ACI. At a later date, diffusion-weighted imaging was available in our institution (and was used additionally in patients no. 8 and no. 9) and allowed early diagnosis in the first week of life. However, as bleeding due to a vascular malformation could not be ruled out after the first MRI scan in one patient, the possible need for subsequent scans should be kept in mind. Regarding neurological outcome, we found that two-thirds of our patients suffered from hemiparesis and five out of nine children showed delayed language development, mostly because of deficits in expressive language. While the frequency of hemiparesis is consistent with the literature, there are few data on language development after neonatal ACI [10]. The majority of our patients need special care facilities and use multiple therapeutic interventions, such as physiotherapy, occupational therapy, speech therapy and special educative support, which underlines the long-term impact of neonatal ACI on the lives of affected patients and families, as well as healthcare resources.

In conclusion, this retrospective case series shows that in our population the incidence of unilateral ACI in newborns is higher than previously reported. The true incidence may even be higher than 1:2300, as not all affected infants have seizures and neurological sequelae. Seizures in the first 3 days of life and pathologic EEG findings should lead to early MRI, regardless of normal cerebral ultrasound, as ACI may be the diagnosis.

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