Epidemiologia e Clinica dello Stroke in fase Neonatale

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R.I.T.I.

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DONA ONLINE

Ogni anno, almeno 1 neonato su 4000 è colpito da malattie da trombosi, quali l'Ictus cerebrale e l'Embolia arteriosa

Il Registro Italiano Trombosi Infantile nasce dal bisogno di condividere i problemi relativi alla **diagnosi**, alla **terapia** e alla **ricerca** delle cause delle malattie da Trombosi nel neonato, nel bambino e nell'adolescente.

Sull'esempio di quanto realizzato in Canada, ALT, a partire dal 2008, ha finanziato e messo a completa disposizione di tutti gli specialisti del settore un registro online in cui poter raccogliere tutti i casi rilevanti, al fine di:

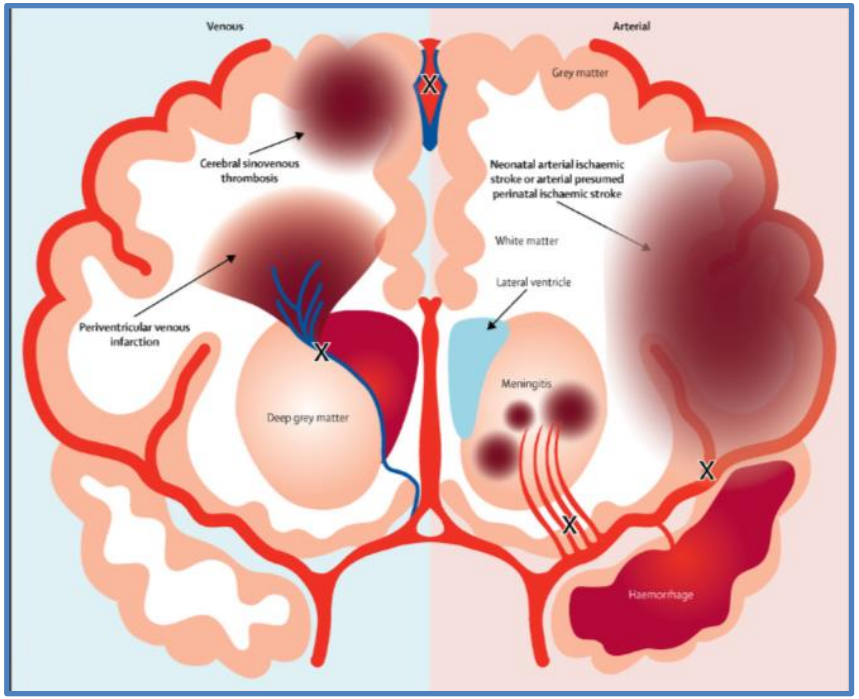
- valutare la rilevanza clinica del problema
- definire le caratteristiche epidemiologiche della Trombosi Infantile
- promuovere la ricerca italiana sulla Trombosi Infantile
- migliorare l'assistenza ai bambini affetti da Trombosi attraverso lo sviluppo di protocolli diagnostici e terapeutici dedicati
- creare un network di medici esperti nell'assistenza a questi pazienti, che possa divenire un punto di riferimento per poter discutere i casi complessi.

R.I.T.I
REGISTRO ITALIANO TROMBOSI INFANTILE

Medici in rete per la diagnosi e terapia delle trombosi infantili

A oggi, il Registro Italiano Trombosi Infantile conta:

- **651 episodi**
- **177 medici iscritti**



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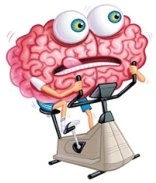
Epidemiologia e Clinica dello Stroke in fase Neonatale : definizione



AHA/ASA Scientific Statement

Management of Stroke in Neonates and Children

A Scientific Statement From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

The standard adult definition of stroke—an acute onset neurological sign or symptom attributable to focal brain infarction or hemorrhage—applies to children as reflected by the National Institutes of Health (NIH) Common Data Elements definition.[1,2]

Lo stroke → sindrome clinica caratterizzata dalla presenza di un deficit neurologico e dall'evidenza neuroradiologica di una lesione ischemica o emorragica di un vaso cerebrale

Stroke. 2019;50:e51–e96

Stroke

Perinatale

Si verifica tra la 20°sett. di e.g. e il 28° giorno di vita postnatale

Pediatrico

Si verifica dal 28° giorno di vita postnatale e il 18° anno di vita

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Stroke Perinatale

Anatomopatologia

1- Stroke arterioso perinatale ischemico (PAIS)
(area infartuale conforme al territorio di occlusione arterioso)

2- Trombosi seni venosi (CSVT)

3- Stroke emorragico (emorragia subaracnoidea, intraventricolare, parenchimale)

4- Infarto periventricolare (infarto della sostanza bianca periventricolare, spesso associato ad evidenza di GMH)

Govaert P, Ramenghi L, Taal R, et al. Diagnosis of perinatal stroke II: mechanisms and clinical phenotypes. Acta Paediatr 2009; 98:1720

Development and the National Institute of Neurological Disorders and Stroke. Pediatrics 2007; 120:609.

Raju TN, et.al Perinatal Stroke Workshop Participants . Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics 2007

Stroke Perinatale

Area di danno tissutale cerebrale determinata dall'interruzione del flusso ematico in una delle maggiori arterie (trombosi o embolismo PAIS)/vene cerebrali (trombosi CSVT)

Fisiopatologica

1- Stroke arterioso perinatale ischemico (PAIS)

2- Trombosi seni venosi (CSVT)

Raju TN, et.al Perinatal Stroke Workshop Participants . Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics 2007

Stroke Perinatale

A- ***Stroke ischemico fetale***: diagnosi prima della nascita mediante neuroimmagini o all'esame autoptico postnatale

B- ***Stroke ischemico neonatale***: diagnosi alla nascita fino al 28° giorno di vita postnatale (includendo neonati pretermine)

C- ***Presunto stroke ichemico perinatale (PPIS) :***diagnosi dopo il 28° giorno di vita postnatale ma con presunto evento ischemico verificatosi nel periodo perinatale

Nelson KB. Perinatal ischemic stroke. Stroke 2007 ; 38 : 742 – 5

Epidemiologia e Clinica dello Stroke in fase Neonatale : epidemiologia

- Incidenza PAIS: 1 su 2.300- 4.000 parti
- Incidenza CSVT: 1-2.69 per 100.000 neonati
- 15% dei neonati con PAIS sono pretermine
- Incidenza maggiore in neonati con e.g. tra 37-40 sett.

- L' incidenza di entrambe le condizioni è sottostimata a causa di una presentazione clinica non specifica e a causa di una "misdiagnosis" alle neuroimmagini

-Berfelo FJ, Kersbergen KJ, van Ommen CH, et al. Neonatal cerebral sinovenous thrombosis from symptom to outcome. Stroke 2010 ; 41 : 1382 – 8

Ramenghi LA, Govaert P, Fumagalli M, et al. Neonatal cerebral sinovenous thrombosis. Semin Fetal Neonatal Med 2009 ; 14 : 278 – 83

Epidemiologia e Clinica dello Stroke in fase Neonatale : epidemiologia

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This scientific statement represents a synthesis of data and a consensus of the leading experts in childhood cardiovascular disease and stroke.

Overview of Childhood and Perinatal Stroke

Introduction and Definition

The standard adult definition of stroke—an acute onset neurological sign or symptom attributable to focal brain infarction or hemorrhage—applies to children as reflected by the National Institutes of Health (NIH) Common Data Elements definition.[1,2] However, in the neonatal period, the acute presentation can be missed. Thus, it is important for pediatric health professionals to be able to recognize stroke at different ages and to treat stroke to preserve brain function and to promote repair and recovery.

Classification

There are different ways of characterizing pediatric stroke. One is by age: Stroke occurring from 28 weeks' gestation to 28 postnatal days of life is broadly classified as perinatal stroke, and stroke occurring after 28 days to 18 years of age is classified as childhood stroke. Within perinatal stroke, mode of presentation distinguishes 2 varieties. Acute perinatal stroke occurs in newborn infants at or near birth and typically presents shortly after onset with focal seizures or encephalopathy.

Epidemiology

Perinatal Stroke

Arterial ischemic infarction accounts for ≈80% of perinatal strokes. The remainder are caused by CSVT or hemorrhage (excluding subarachnoid hemorrhage [SAH] and intraventricular hemorrhage [IVH] in premature babies). Ischemic stroke occurs in up to 1 in 3500 newborns, although some estimates are as low as 1 in 10 000 newborns.[7–9] The ratio of ischemic stroke is dramatically higher in newborns, almost 6 times greater than in older children.[8]

Agarwal and colleagues[9] identified 60 individuals with perinatal stroke among a cohort of 208 876 live births. This represents a frequency of 29 in 100 000 live births, or 1 per 3500 live births. Their overall stroke rate for both ischemic and hemorrhagic stroke was 37 per 100 000 live births, or 1 per 2700 live births.[9]

Armstrong-Wells et al[10] identified 19 infants with hemorrhagic stroke and 1 with SAH among 323 532 live births in the Northern California Kaiser-Permanente Medical Care program, representing a population prevalence for perinatal hemorrhagic stroke of 6.2 per 100 000 live births. Cole et al[11] calculated the incidence of perinatal hemorrhagic stroke as 1 per 6300 live births for both hemorrhage and hemorrhagic infarction.

Epidemiologia e Clinica dello Stroke in fase Neonatale : epidemiologia

Perinatal Ischemic Stroke

Karin B. Nelson, MD

Abstract—Perinatal ischemic stroke is not rare in term and near-term infants and is an important antecedent of long-term neurological disability, including congenital hemiplegia (hemiplegic cerebral palsy) and seizure and cognitive disorders. Changes in maternal hemostasis occur in pregnancy and are amplified in the period immediately surrounding birth; stroke and other thromboembolic events are more frequent in both mother and infant in this period. The vasculature and hemostatic mechanisms of placenta as well as brain are likely to be important in the pathobiology of perinatal stroke. Maternal and infant thrombophilias, genetic and acquired, play a role. Rarely is >1 child in a sibship affected, and environmental factors—substantially less studied, to date—are likely to be key determinants of risk. **(*Stroke*. 2007; 38[part 2]:742-745.)**

Key Words: hemiplegic cerebral palsy ■ perinatal stroke

"A large number of cases of infantile cerebral palsy are caused by the same factors that bring about the majority of cases of cerebral paralysis of adults: tearing, embolism, and thrombosis of cerebral vessels."[1]

The 2 periods of life in which the risk of having a stroke is highest are in the elderly and in the fetus or newborn infant. In both these periods, stroke is associated with heightened risk of death or, in survivors, of persisting neurological disability.

It was recognized long ago on the basis of autopsies in newborn infants that perinatal arterial ischemic stroke (PAS) can occur and is not extremely uncommon. The advent and increasing use of neuroimaging in young children permitted identification of PAS in surviving children and led to recognition of the relatively high frequency of PAS and its high morbidity. Clinical features of stroke in the perinatal age group, risk factors for its occurrence, and natural history, including outcome, are increasingly, although still imperfectly, known.

Why does stroke in the fetus or newborn warrant inclusion at the Princeton Conference, a gathering that focuses on stroke in adults? The freedom of the neonate from comorbidities that feature so prominently in stroke in the adult, such as atherosclerosis, diabetes, hypertension, and smoking, permits a view of the neurovascular processes underlying ischemic stroke in the newborn in relatively pure culture. The

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Definition and Incidence

PAS is a cerebrovascular event occurring during fetal or neonatal life, before 28 days after birth, with pathological or radiological evidence of focal arterial infarction of brain. As used here, the term excludes hemorrhagic stroke, generalized ischemic lesions in arterial border zones, and cerebral venous thromboses. In the newborn, unlike the older child or adult, there are no clinical signs that permit even a presumptive diagnosis of perinatal stroke; recognition rests on neuroimaging.

Estimates of the frequency of PAS vary with the frequency of use of CT or MRI. In a recent population-based study with relatively frequent neuroimaging, unilateral PAS was recognized in the neonatal period in 1 in 2300 term infants.[2] Bilateral strokes are not uncommon, and not all infants were imaged, however, and this prevalence figure does not include children whose PAS was first identified after the newborn period (see below).

Stroke is 17 times more common in the perinatal period than later in childhood or beyond.[3] In the only available population-based study of perinatal stroke that included children whose perinatal stroke was diagnosed after the first months of life,[4] the rate of perinatal stroke was 1:5000, at least as high as the annual incidence of large-vessel ischemic stroke in adults (17 to 23 per 100 000).[5] Thrombosis at other sites also concentrates in the perinatal period.

Epidemiologia e Clinica dello Stroke in fase Neonatale : fisiopatologia

La trombosi dei vasi placentari si verifica normalmente alla fine della gravidanza e gli emboli possono essere rilasciati nella circolazione fetale alla nascita

Inoltre,la patologia placentare può portare

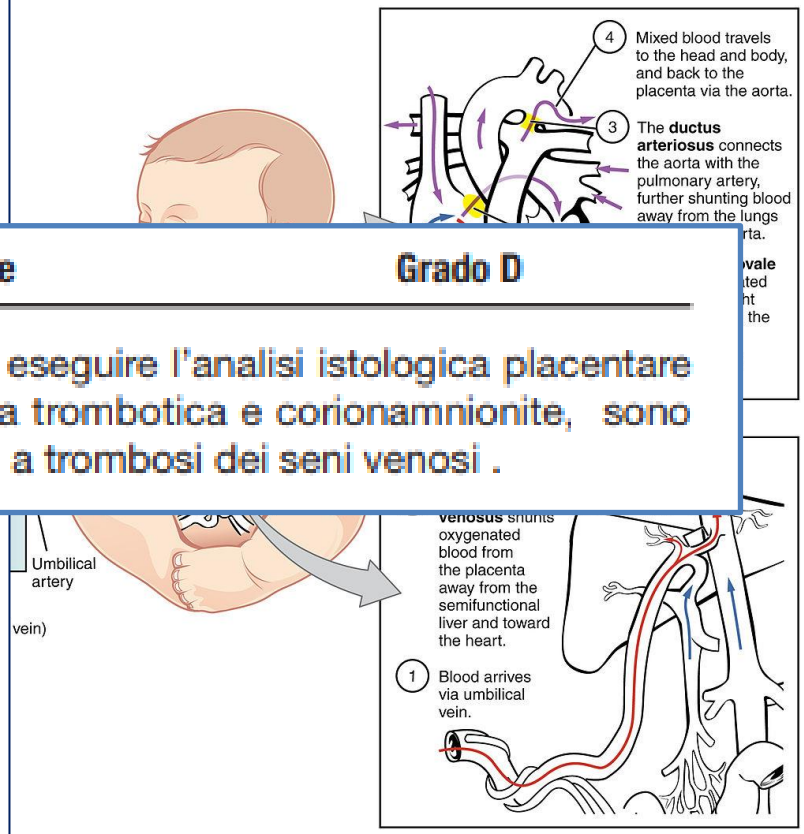
Raccomandazione 16.1 **Forte a favore** **Grado D**

In tutti i casi di ictus perinatale è raccomandato eseguire l'analisi istologica placentare in quanto alterazioni placentari, quali vasculopatia trombotica e corionamnionite, sono risultate essere associate sia a ictus arterioso che a trombosi dei seni venosi .

- I coaguli venosi possono attraversare il forame ovale pervio e dirigersi verso vasi cerebrali arteriosi

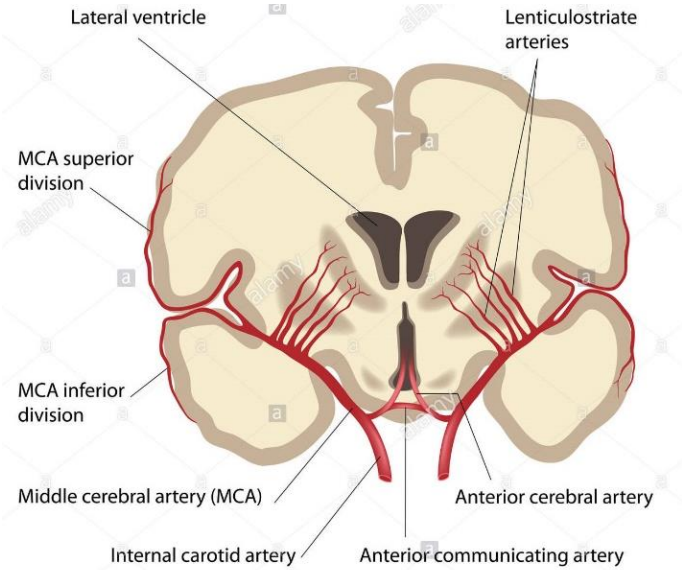
- Shunt destro-sinistro nelle cardiopatie congenite→ consente agli emboli di entrare nella circolazione cerebrale

- Emboli possono derivare da trombi che si sviluppano lungo il decorso del CVO



Stroke arterioso ischemico (AIS)

l'arteria cerebrale media (MCA) è il vaso maggiormente coinvolto



Distribuzione anatomica AIS mediante studio di coorte con 166 PAIS confermati dalla risonanza magnetica:

- 51% delle arterie cerebrali media
- 19% arteria cerebrale anteriore
- 18 % arteria cerebrale posteriore
- 9 % infarti cerebellari

Lequin MH, Peeters EA, Holscher HC, et al. Arterial infarction caused by carotid artery dissection in the neonate. Eur J Paediatr Neurol 2004 ; 8 : 155 – 60

Epidemiologia e Clinica dello Stroke in fase Neonatale MCA

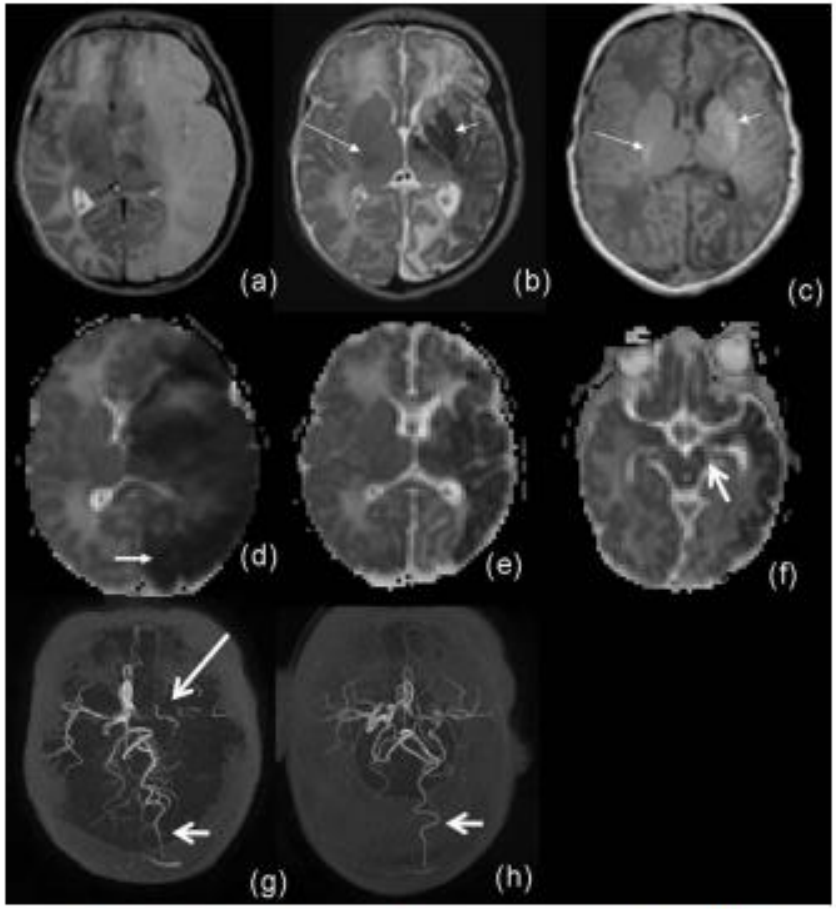


Figure 1 Large left sided middle cerebral artery infarct. Term neonate imaged with T2 weighted (A and B), T1 weighted (C), diffusion weighted (D–F) and MR angiogram (G and H) sequences at 3 days (A,D,G) and again at 10 days (B,C,E,H). At 3 days there is widespread loss of grey white matter differentiation in the left cerebral hemisphere with swelling and midline shift (A). The diffusion weighted imaging ADC map (D) shows extensive restricted diffusion seen as low signal intensity in the territory of the left MCA and also in adjacent tissue normally supplied by the posterior cerebral artery (arrow) D. At 10 days the swelling has subsided and there is no longer any midline shift (B and C). There is now abnormal signal intensity within the left hemispheric white matter and cortex with an exaggeration of contrast in the basal ganglia (short arrows) and thalami (BGT) and the posterior limb of the internal capsule (PLIC) (B and C). The PLIC on the right has a normal appearance (B and C) (long arrows). There is still restricted diffusion although this has decreased (E and F), there is focal low signal in the left cerebral peduncle (arrow) (F). This infarct involves three sites, hemisphere, BGT and PLIC involvement and abnormal signal intensity on the brainstem on diffusion and is likely to be associated with a later hemiplegia.[29,31] On MR angiogram there is initially asymmetry with marked reduction in flow through the left middle cerebral artery (MCA) and its branches (G) (long arrow). These are more obvious on day 10 (H). There is a unilateral long branch of the posterior cerebral artery on the left seen at 3 and 10 days (G and H) (short arrows).

PAIS MCA sinistra in neonato a termine:

- di 3 giorni di vita: A-D-G→ perdita della differenziazione della SB e SG emisfero sx, edema e spostamento LM

-10 giorni di vita: B-C-E-H→ atrofia corticale, poroencealia

Epidemiologia e Clinica dello Stroke in fase Neonatale : MCA

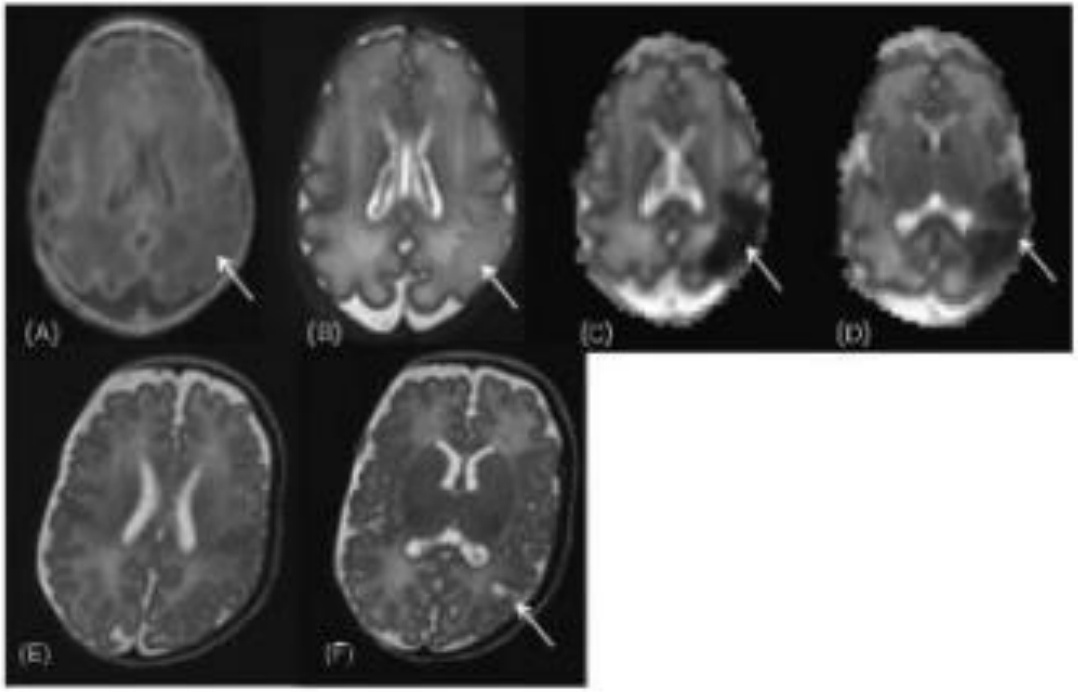


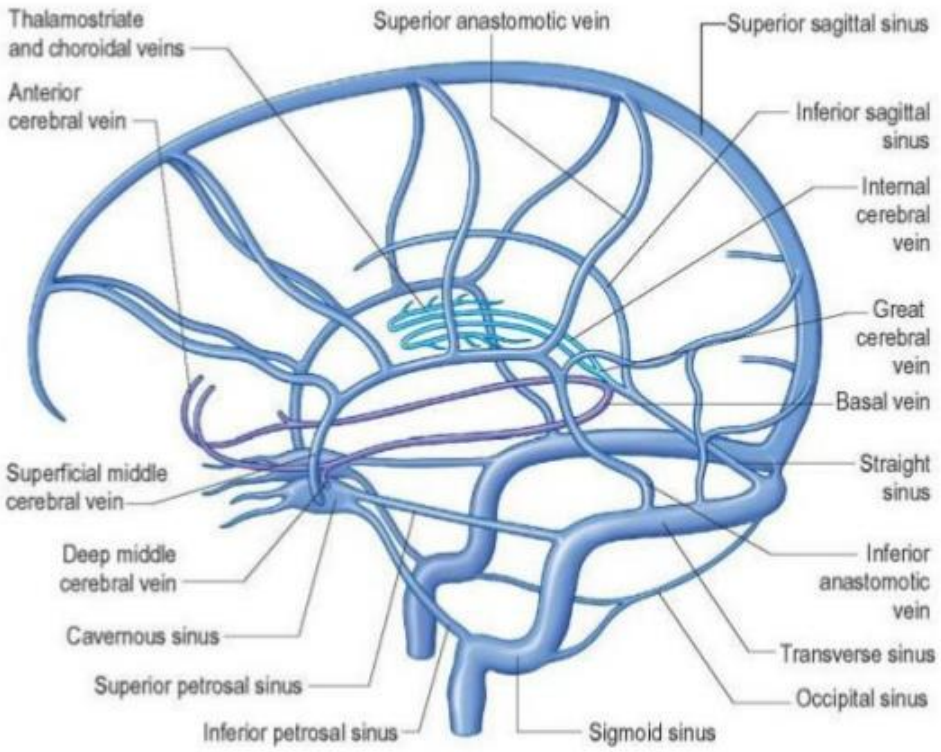
Figure 2 Left sided middle cerebral artery infarct in an infant born at 30 weeks gestation and imaged at 3 days of age (top row) and again at 40 weeks postmenstrual age (bottom row). T1 weighted (A), T2 weighted (B,E,F) and diffusion apparent diffusion coefficient (ADC) maps (C and D). At 3 days of age the abnormalities on conventional T1 (A) and T2 (B) weighted imaging are still subtle with some loss of grey white matter differentiation (arrows). The changes on the ADC map at a high ventricular and basal ganglia level are more striking (C and D). The low signal intensity indicates restricted diffusion with a low, ADC consistent with ischaemia. At 40 weeks PMA (E and F) there is no ventricular dilation and subtle tissue loss with an enlarged sulcus most obvious at the level of the basal ganglia (F) (arrow). The basal ganglia, thalami and PLIC are symmetrical and of normal appearance for age. The child has a normal motor outcome at two years of age.

PAIS MCA sinistra in neonato a pre-termine 30 set eg:

- di 3 giorni di vita: A-D-G→ perdita della differenziazione della SB , alterata diffusione dei nuclei della base
-40 sett: E-F→ no dilatazione ventricolare, non alterazione nuclei della base
Outcome motorio a 2 anni: normale

CSVT

infarto parenchimale secondario a drenaggio venoso alterato



Epidemiologia e Clinica dello Stroke in fase Neonatale : patofisiologia

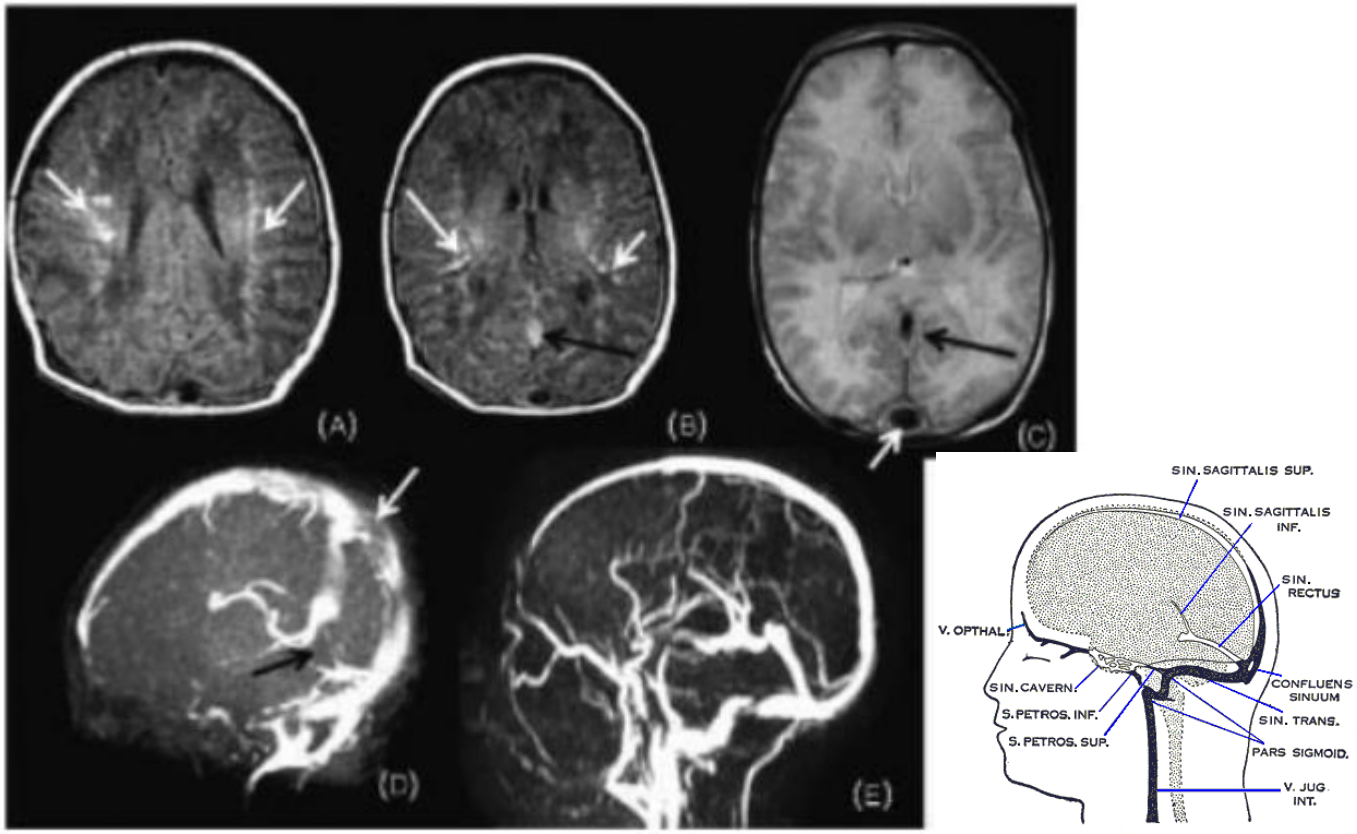


Figure 3 Sagittal and straight sinus thrombosis. Term born neonate with hypoxic-ischaemic encephalopathy. T1 weighted (A and B) and T2 weighted (C) images in the transverse plane. There are multiple areas of cortical highlighting (arrows) (A and B). There is abnormal signal intensity within the straight sinus seen as high signal intensity on the T1 weighted image (black arrow) (B) and low signal intensity on the T2 weighted image (black arrow) (C). There is additional low signal intensity within the torcula (white arrow) (C). The venogram (D) shows patchy filling in the sagittal sinus (white arrow) and straight sinus (black arrow). A normal venogram is shown for comparison in (E).

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Review

Neonatal stroke

M A Rutherford,[1,2] L A Ramenghi,[3] F M Cowan[2,4]

Epidemiologia e Clinica dello Stroke in fase Neonatale : patofisiologia

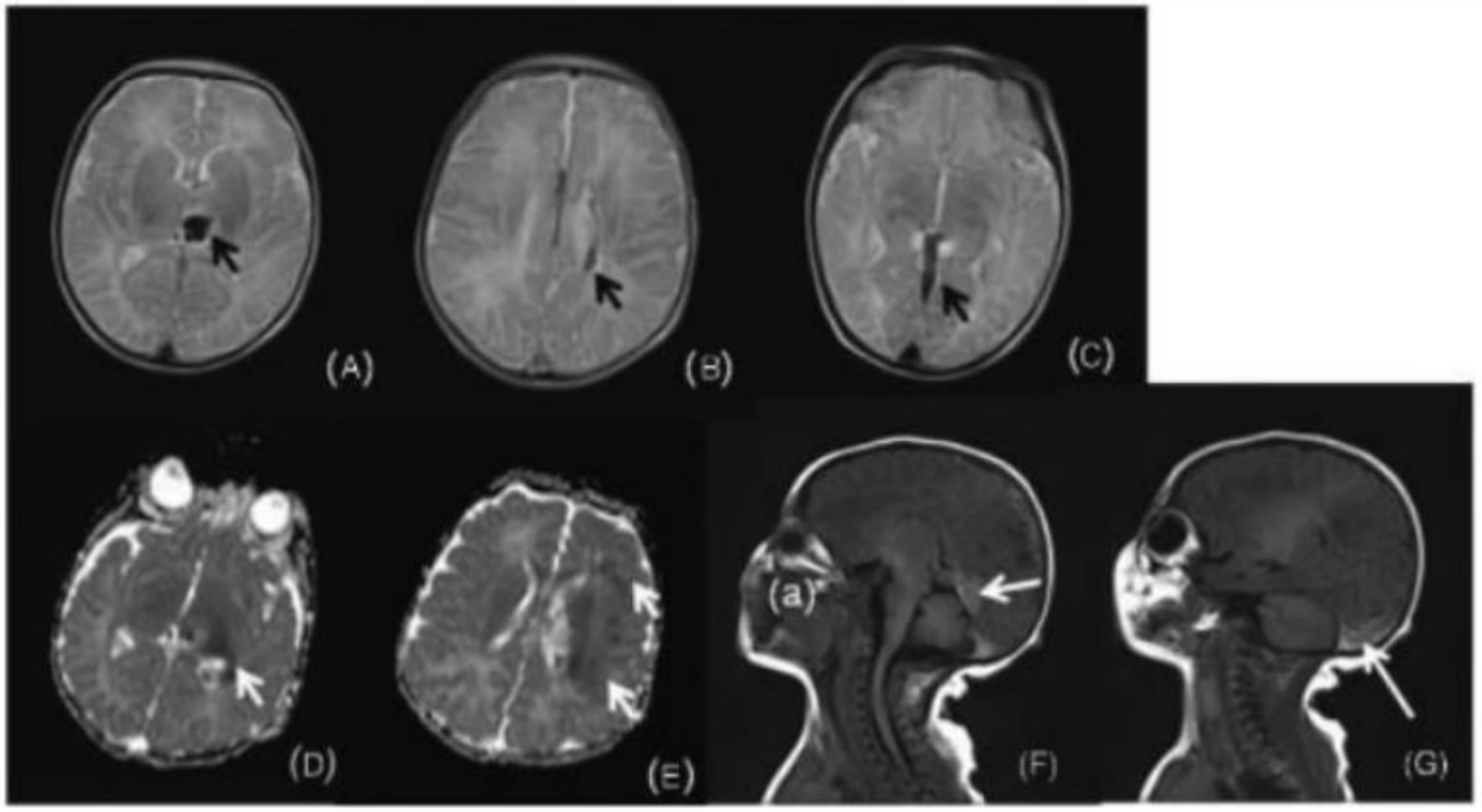

Figure 4 Thalamic haemorrhage. Term born neonate born to a mother with gestational diabetes, by emergency caesarean section following a failed forceps extraction and presenting with right sided seizures at 8 days of age. Left sided bruise noted on face. No signs of sepsis but dehydrated with a 10% weight loss since birth. Imaging at 9 days of age with T2 weighted images (A-C), Apparent diffusion coefficient (ADC) maps (D and E) and sagittal T1 weighted images (F and G). There is thrombosis seen as low mixed signal intensity on T1 weighted images in the straight (F) (arrows) and sagittal sinu haemorrhagic lesion in the left thalamus (A) (arrow). There is a distended vessel at a high there is additional low signal intensity in the left posterior thalamus and around the poster to the ventricle and at the depths of sulci. (E) (arrows) indicating additional ischaemic injur

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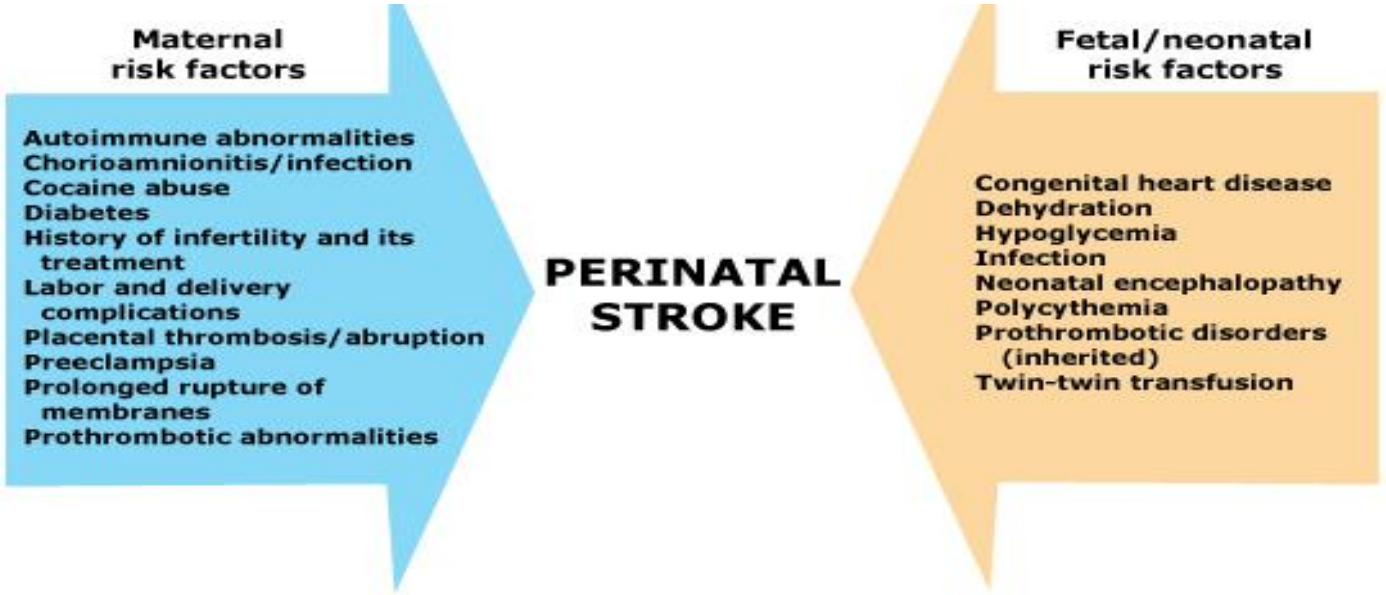
Review

Neonatal stroke

M A Rutherford,[1,2] L A Ramenghi,[3] F M Cowan[2,4]

Epidemiologia e Clinica dello Stroke in fase Neonatale : eziologia



variants.

While pregnancy itself is a prothrombotic state, additional pre-existing maternal factors linked with PAIS include autoimmune disorders, infertility, in utero cocaine exposure, maternal trauma and maternal infection.[25]

A study of multiple risk factors found that a history of infertility and pre-eclampsia were independent risk factors for PAIS, and the presence of more than one risk factor increases the probability of PAIS from 1 in 1000 to 1 in 200.[26] However, this study included term infants with neonatally symptomatic PAIS, infants with PPIS and preterm infants. Pre-eclampsia has been identified as an independent risk factor in some but not all studies.[10] Pre-eclampsia is attributed to reduced uteroplacental blood flow as a consequence of a vascular defect in

CSVT.[12 17]

Placental disorders including thrombosis, abruption, infection and feto-maternal haemorrhage may be under diagnosed in perinatal stroke because placentas are often not adequately examined or discarded before the infant becomes symptomatic.

Fetal disorders that predispose to PAIS include twin pregnancies with or without co-twin demise and twin-to-twin transfusion syndrome.[15 28] Cardiac disorders represent a risk factor for both PAIS and CSVT. In one study of CSVT, 26% of neonates had a cardiac defect,[17] but these are seldom found in others reflecting the difference in populations studied. The neonate with a cardiac defect is at risk of brain injury, perinatally, following balloon septostomy and perioperative-

Epidemiologia e Clinica dello Stroke in fase Neonatale : eziologia

Mode of delivery

There is a high intervention rate in PAIS with few cases born by elective prelabour caesarean section.[25] High rates (60%) of complicated deliveries, instrumental or emergency caesarean section are reported. In the preterm infant the presence of AIS has been associated with a history of fetal heart rate abnormalities during labour.[15] Complicated deliveries are also common, with rates of up to 25% in neonates with CSVT.[12 17 31]

Neonatal factors

Signs of fetal compromise are common in neonates with PAIS and arterial infarction has been reported in association with HIE,[32] but there were no cases of PAIS in one large study with strict entry criteria for HIE.[33] Hypoglycaemia was shown to be independently associated with AIS in the preterm infant,[15] although in the term infant it is usually associated with a bilateral parasagittal or watershed pattern of infarction.[6]

The neonate with CSVT may present with poor feeding, weight loss and dehydration with or without suspected sepsis.[12 17 31] The most widely reported additional pathologies are meningitis[31] or non-central nervous system sepsis (10% and ~15% respectively) (figure 5). CSVT appears to be less common in HIE at approximately 3%,[33] although perinatal compromise was reported in 57% of 30 neonates with CSVT in one study.[27] Meningitis is also a risk factor for PAIS.[10 34] Neonates treated with extracorporeal membrane oxygenation for severe respiratory pathology are at high risk of cerebral infarction.[35] Most reports indicate that male infants are more susceptible to both PAIS and CSVT.[10 11 17 31 36]

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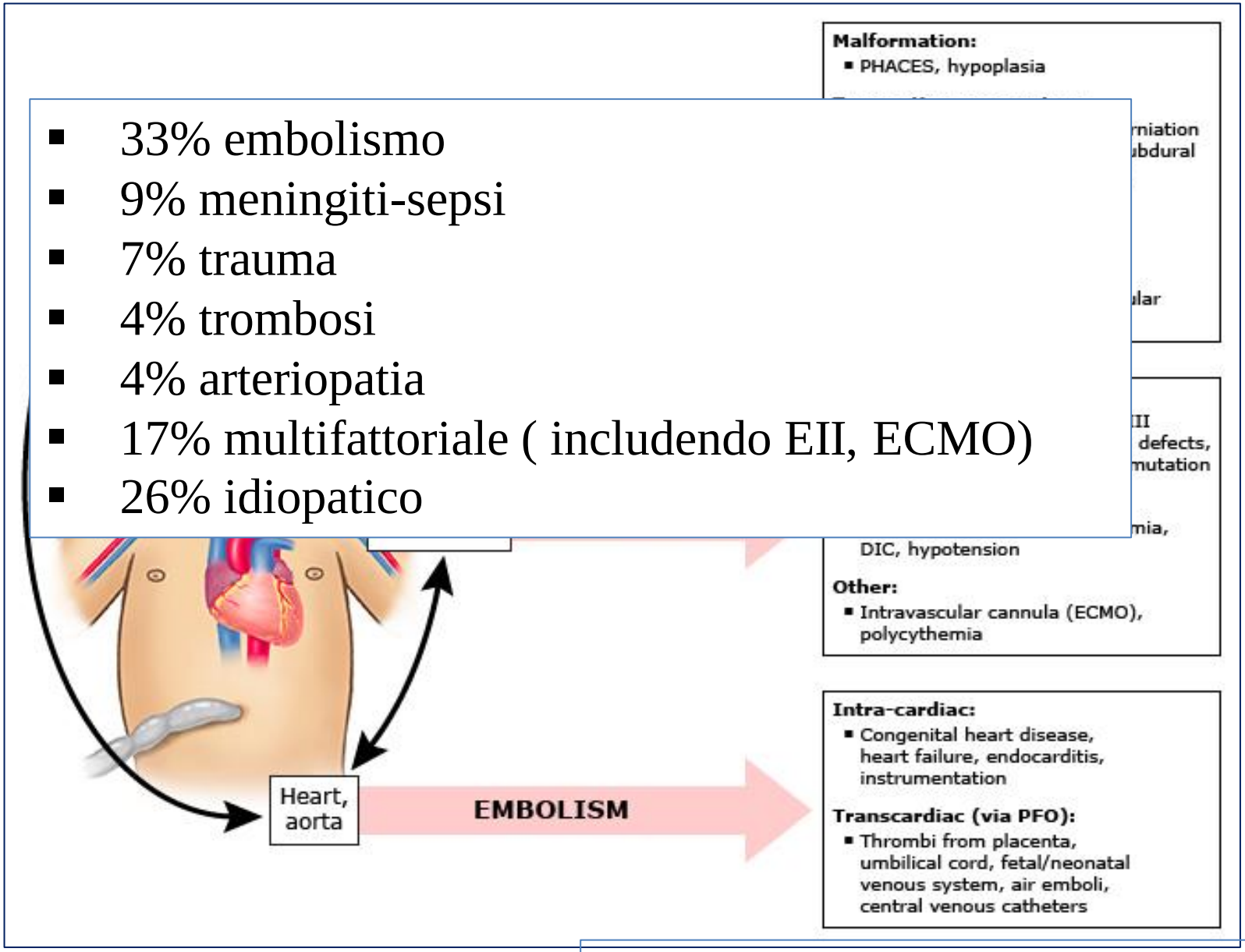
Epidemiologia e Clinica dello Stroke in fase Neonatale : eziologia

- 33% embolismo
- 9% meningiti-sepsi
- 7% trauma
- 4% trombosi
- 4% arteriopatia
- 17% multifattoriale (includendo EII, ECMO)
- 26% idiopatico



Govaert P, Ramenghi L, Taal R, et al. Diagnosis of perinatal stroke II: mechanisms and clinical phenotypes. Acta Paediatr 2009; 98:1720

Fattori di Rischio

Fattori protromboici in PAIS (range 42–78%)

Mutazione COL4A1 subunità del collagene di tipo IV che gioca ruolo in angiogenesi

Raccomandazione 16.2 **GPP**

In tutti i casi di ictus perinatale è indicato eseguire un dettagliato screening trombofilico sia nel neonato che nella madre che includa la ricerca degli anticorpi antifosfolipidi, la lipoproteina (a) ed indagini atte ad escludere una trombofilia ereditaria in particolare il dosaggio di proteina C, proteina S, antitrombina III, mutazione del fattore V Leiden e della protrombina.

FVL G1691A e rischio 3.8 volte maggiore in madri con la mutazione del fattore II G20210A

Curry et al→ eterozigosi o omozigosi per la mutazione MTHFR C677T, trovata in 41/60 neonati (68%).
La SOLA mutazione del gene MTHFR non aumenta il rischio di trombogenesi se non associate ad elevate livelli di omocisteina

Review multicentrica in neonati con CVST→ mutazione MTHFR in 13/23 ma tutti con normali livelli di omocisteinemia

Raccomandazione :

Nei bambini con stroke ischemico va eseguita valutazione cardiologica con ECG ed ecocardiografia

RACCOMANDAZIONE GRADO A LIVELLO DI EVIDENZA V-VI

Malattie cardiache congenite	Malattie cardiache acquisite
Coartazione	Cardiomiopatia e miocardite
Difetti complessi congeniti	Disaritmie
Difetti settali ventricolari/atriali	Endocardite batterica
Pervietà del dotto arterioso	Malattia reumatica
Pervietà del forame ovale	Mixoma atriale
Stenosi aortica o mitralica	Rabdomioma cardiaco
	Valvola cardiaca protesica

Epidemiologia e Clinica dello Stroke in fase Neonatale : clinica AIS

Neonati con AIS→ di solito non richiedono rianimazione neonatale
sebbene il travaglio e il parto siano spesso complicati

Maggiore incidenza → Sesso Maschile
L'insorgenza di crisi si verifica in genere il primo giorno dopo la nascita
Tempo medio di esordio clinico: 90% dei casi entro 3 giorni

Esordio della clinica ex abrupto:

- ***Convulsioni***
- Apnea
- Letargia
- Ipotonia
- Irritabilità
- difficoltà alimentazione

Nei neonati pretermine AIS può essere diagnosticato durante l'esecuzione routinaria di ecografia cerebrale → incidentale

Epidemiologia e Clinica dello Stroke in fase Neonatale : clinica AIS

Le convulsioni sono il sintomo presente o predominante nel 48-88%

Convulsioni : 94% AIS neonatale **vs** 17% AIS pediatrico

Convulsioni→ motorie focali interessando una sola estremità, tipicamente controlaterali all'emisfero interessato nei neonati con AIS unilaterale

Emisfero cerebrale sinistro→ 80% stroke unilaterali; territorio arteria cerebrale media (MCA)

In uno studio retrospettivo su neonati con convulsioni a cui era stato diagnosticato un ictus ischemico arterioso (n = 27) o encefalopatia ipossico-ischemica (n = 35), la presenza di convulsione ≥ 12 ore dopo la nascita e le convulsioni motorie focali erano predittori indipendenti di ictus

Common etiologies of neonatal seizures

Hypoxic-ischemic encephalopathy
Ischemic stroke
Arterial
Venous
Intracranial hemorrhage
Intraparenchymal
Intraventricular
Subarachnoid
Subdural
Central nervous system infection
Meningitis
Encephalitis
Intrauterine (prenatal) infection
Metabolic disturbance
Hypoglycemia
Hypocalcemia
Hypomagnesemia
Neonatal-onset epilepsy
Epileptic encephalopathy/genetic epilepsy syndrome
Congenital brain malformation
Benign familial neonatal epilepsy
Inborn error of metabolism

van der Aa NE, Dudink J, Benders MJ, et al. Neonatal posterior cerebral artery stroke: clinical presentation, MRI findings, and outcome. Dev Med Child Neurol 2013; 55:28.
deVeber GA, Kirton A, Booth FA, et al. Epidemiology and Outcomes of Arterial Ischemic Stroke in Children: The Canadian Pediatric Ischemic Stroke Registry. Pediatr Neurol 2017; 69:58.

Epidemiologia e Clinica dello Stroke in fase Neonatale : clinica AIS

- Molti bambini con lesioni unilaterali hanno un'emiparesi, anche se questo può essere difficile da rilevare se non dal clinico più esperto.
- L'emiparesi può apparire come asimmetria di movimenti spontanei.
- Tuttavia, l'emiparesi causata da AIS perinatale viene diagnosticata per la prima volta nell'infanzia (***mediana di sei mesi***) in alcuni pazienti dopo un normale decorso neonatale
- Riflessi primitivi, come i riflessi del collo tonico e Moro, possono essere esagerati.

- Deficit sensoriali possono verificarsi se coinvolti→ i lobi parietali e occipitali
- AIS → dell'arteria cerebrale posteriore determina frequentemente un difetto del campo visivo come un'emianopsia omonima o quadrantopsia

- Le lesioni diencefaliche possono causare un controllo della temperatura disturbato e cicli di sonno-veglia

Epidemiologia e Clinica dello Stroke in fase Neonatale : clinica CSVT

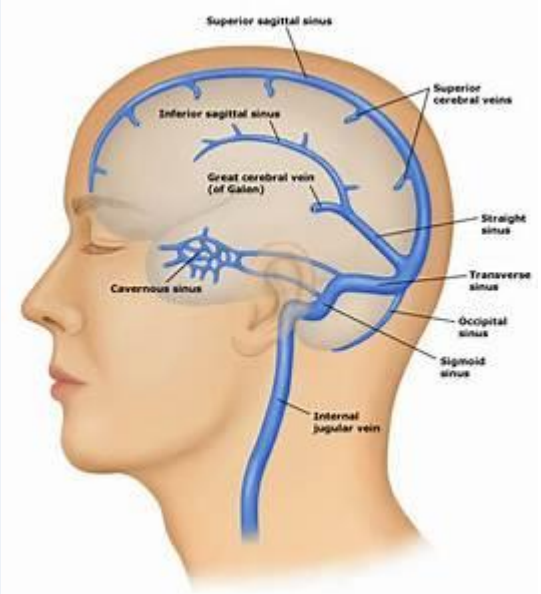
Spesso clinica non specifica come segni neurologici quali letargia/irritabilità→ 58% dei casi

Segni neurologici focali (emiparesi,paralisi nervi cranici)→ 29% dei casi

Tra i 69 neonati con CSVT nel registro canadese, le convulsioni focali o generalizzate si sono verificate nel 71%

Nel Registro canadese per StroKE Pediatrico:

→ Più colpiti: seno sagittale 62 %, seno retto 39%



EMORRAGIA CEREBRALE INTRAVENTRICOLARE IN NEONATO A TERMINE

Edema cerebrale e aree di infarto emorragico, che coinvolgono in particolare la sostanza bianca periventricolare, accompagnano frequentemente il CSVT.

→ Circa il 50% dei neonati con CSVT ha esordio clinico entro 48 ore di vita ;
→ Il 25% dei neonati con CSVT ha esordio clinico entro la prima settimana di vita;

Epidemiologia e Clinica dello Stroke in fase Neonatale : diagnosi

Test per trombofilia
Diminuiti livelli Proteina C, Proteina S, antitrombina
Aumentati livelli Fattore VIII, IX,XI,Fibrinogeno,Lipoproteina(a),omocisteina
Anticorpi antifosfolipidi
Lupus anticoagulant
Fattore V di Leiden
Fattore II G20210A
MTHFR C677T

Livelli di Proteina C, Proteina S, antitrombina e fattore XI → normalmente ridotto al 30% dei livelli degli adulti

Imaging

Ecografia transfontanellare→ l'imaging neonatale e dovrebbe includere l'uso di tutte e quattro le finestre acustiche, la fontanella anteriore e posteriore, temporale e mastoidea

EVOLUZIONE ECOGRAFICA DELLO STROKE:

1° fase: area iperecogena di forma grossolanamente triangolare, margini lineari

2° fase: necrosi con cavitazione del territorio interessato, formazione di sepimenti, lesione poroencefalica

3° fase: atrofia della zona colpita, dilatazione ex vacuo ventricolo omolaterale, atrofia talamo omolaterale, aumento spazi pericerebrali corrispondenti

Imaging -

TC ecencefalo

L'accertamento neuroradiologico di elezione è la RMN

Le problematiche organizzative e la complessità dell'esame spesso, però, ne limitano l'u… diagnosi precoce, è … segni e sintomi sug…

E' da tenere comunque presente che la TC puo' essere completamente negativa nelle prime ore dall'evento

Questo esa… ***…cità nell'evidenziare focolai ischemici, consente di escludere la presenza di eventuali focolai emorragici*** (ESA e/o emorragia intraparenchimale) ***ed eventualmente altre patologie responsabili della sintomatologia*** ("stroke mimics": neoplasie, patologie degenerative, patologie malformative o infettivo-infiammatorie)

Imaging -

RMN encefalo

La RMN è infatti in grado di svelare precocemente la lesione utilizzando, oltre le sequenze routinarie (FLAIR, SE e FFE- T2) , sequenze più sensibili della durata complessiva di circa un minuto come DWI e ADC

Ad una generica richiesta specialistica di "***RMN encefalo in sospetto ictus" , priva di ulteriori specificazioni***, deve corrispondere un protocollo codificato che comprenda sia sequenze pesate in diffusione (DWI e ADC) che sequenze ***Angio-RM arteriose*** *(della durata di circa 4 minuti)* con studio esteso alle diramazioni arteriose distali, per escludere eventuali fistole artero-venose durali (FAVD) e *venose (della durata di circa 2 minuti)*, ***e una angio-RM venosa, qualora si sospetti una trombosi dei seni venosi***

Management AIS

Supportive care: controllo delle convulsioni, l'ottimizzazione dell'ossigenazione e la corr
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Ruolo potenziale di ipotermia terapeutica nei neonati con PAIS o CSVT deve ancora essere determinato, ma l'ipertermia deve essere evitata

L'American College of Chest Physicians (ACCP) raccomanda la somministrazione di eparina non frazionata (UFH) o eparina a basso peso molecolare (LMWH) in
neonati con un primo AIS e una sorgente cardioembolica documentata in corso.
Altrimenti la terapia anticoagulante o antiaggregante

non è raccomandata perché il rischio di recidiva l'ictus è molto basso e non si pensa che la lesione si estenda una volta fatta la diagnosi

Le linee guida ACCP raccomandano:

→il trattamento di neonati con CSVT senza emorragia intracranica significativa, inizialmente con eparina non frazionata (UFH) o eparina a basso peso molecolare (LMWH), seguiti da LMWH o antagonisti della vitamina K per 6-12 settimane

→Per i neonati con CSVT e emorragia significativa, monitoraggio radiologico

Si raccomanda di iniziare la terapia anticoagulante, se si verifica un'estensione del trombo, 5-7 giorni dopo l'emorragia iniziale

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Erythropoietin in Stroke Therapy: Friend or Foe

Rhonda Souvenir[1,2], **Desislava Doycheva**[2], **John H Zhang**[2,3,4], and **Jiping Tang**[2,*]

EPO:
- Neurotrofico
- Angiogenesi
- Anti-apoptotica
- Anti-ossidante

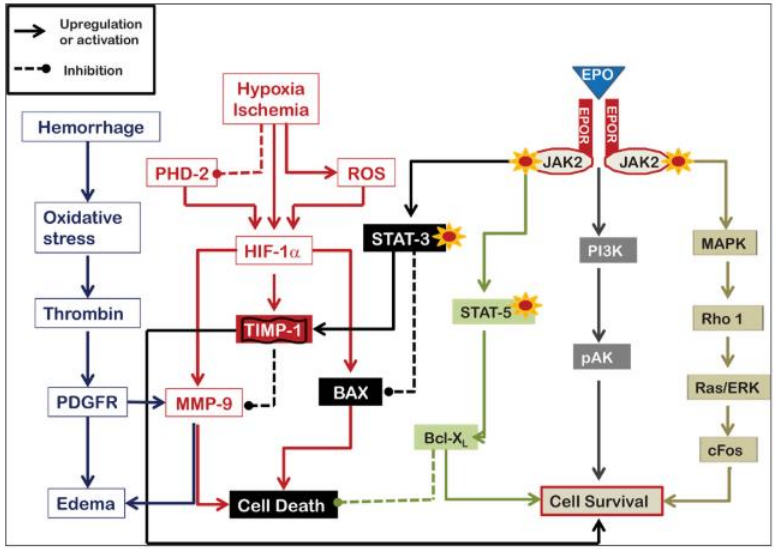

Fig. (1)
Schematic representation of the signaling pathway involved in EPO-induced neuroprotection. The primary mechanisms of secondary injury due to hemorrhagic stroke are presented in blue. One of the primary mechanisms of ischemic injury is presented in red. ...

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Erythropoietin and Neonatal Neuroprotection

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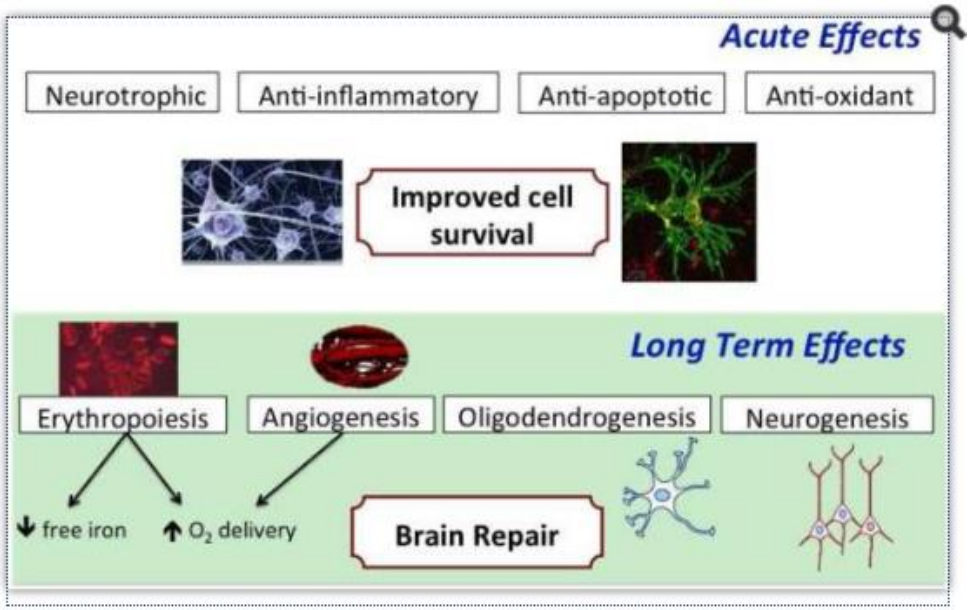

Neuroprotective Effects of Epo: Cell and tissue Repair

The Journal of Pediatrics
Volume 164, Issue 3, March 2014, Pages 481-486.e2

Original Article

Feasibility and Safety of Erythropoietin for Neuroprotection after Perinatal Arterial Ischemic Stroke

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Objective

To perform a feasibility and safety study with recombinant human erythropoietin (rhEPO) in neonates with perinatal arterial ischemic stroke.

Study design

Neonates with a magnetic resonance imaging–confirmed perinatal arterial ischemic stroke (n = 21) were treated with 1000 IU/kg rhEPO immediately after diagnosis and at 24 and 48 hours after the first dose. Repeat magnetic resonance imaging was performed when the patients were 3 months of age. Coagulation and hematologic variables (red blood cells, white blood cells, platelet counts) were performed in the first week after initiation of treatment. We also compared 10 patients who were treated with rhEPO with 10 historic infants with perinatal arterial ischemic stroke matched for the involved arterial branch to investigate whether rhEPO reduces the residual size of the infarction and subsequent brain growth between first and second scan.

Results

Seizures were a first symptom in 20 of 21 neonates. Heart rate, blood pressure, and coagulation function were in the normal range, as were red blood cells, white blood cells, and platelet counts. In a subgroup of 10 rhEPO-treated neonates, no differences were detected in residual infarction volumes or neurodevelopmental outcome compared with their historical nontreated counterparts.

Conclusions

rhEPO in neonates with perinatal arterial ischemic stroke had no adverse effects on red blood cells, white blood cells, platelets counts, or coagulation. rhEPO, 3000 IU/kg in total, given during a 3-day period, appears to be a safe therapy. The beneficial effects remains to be demonstrated in a larger, randomized, double-blind, placebo-controlled trial.

-1000 UI/Kg EPO 3 dosi:

- 1° dopo la diagnosi
- 24°h
- 48°h

→ valutazione: pressione, crasi ematica

Epidemiologia e Clinica dello Stroke in fase Neonatale: conclusioni

- Purtroppo, la letteratura sullo stroke in ambito neonatale è gravemente carente
- Non esistono, inoltre, omogenei comportamenti nell' approccio diagnostico-terapeutico allo stroke ischemico in età neonatale-pediatrica
- Si sente sempre piu' forte, pertanto, la necessità di studi collaborativi multicentrici non solo per valutare con precisione la validità delle terapie piu' adottate , ma anche per tentare, su ampi numeri, nuovi approcci terapeutici

grazie...