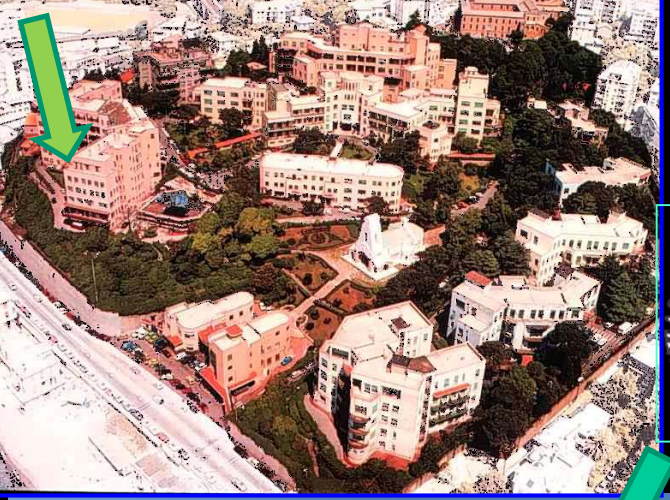
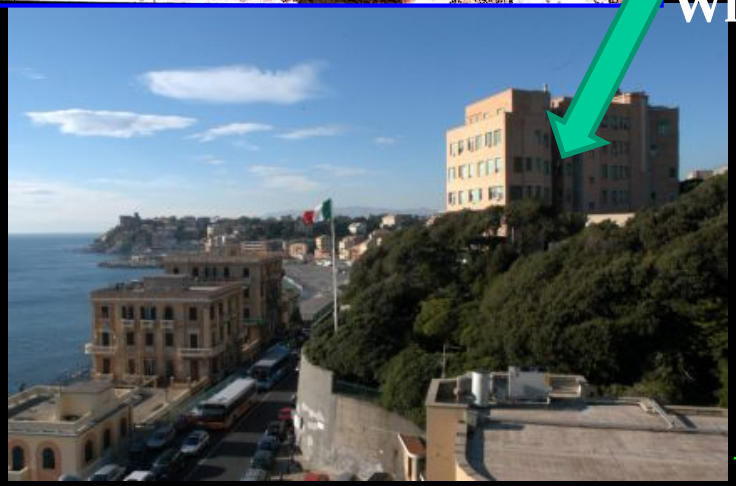


Wing 12



Patologia e Terapia Intensiva Neonatale

Istituto Pediatrico "Giannina Gaslini" IRCCS Genova

IL FIGLIO DI MADRE DIABETICA

Luca A. Ramenghi MD PhD

…la puericultura e' stata collocata dal 1938-39 tra i corsi per gli student di medicina . . .

THE MANAGEMENT OF PREGNANCY AND THE NEWBORN INFANT OF DIABETIC MOTHERS[1]

ROBERT M. GRIER, M.D. and ALVAH L. NEWCOMB, M.D.

The newborn infant of the diabetic woman is usually large, edematous, and icteric. Respiratory embarrassment, instability of the blood sugar and erythroblastosis are often present. These signs and symptoms appear more frequently in the babies of the mothers who have been diabetic for a long period.

[1]From the Department of Obstetrics and Gynecology, and Pediatrics, Northwestern University Medical School.
Received for publication, May 26, 1951.

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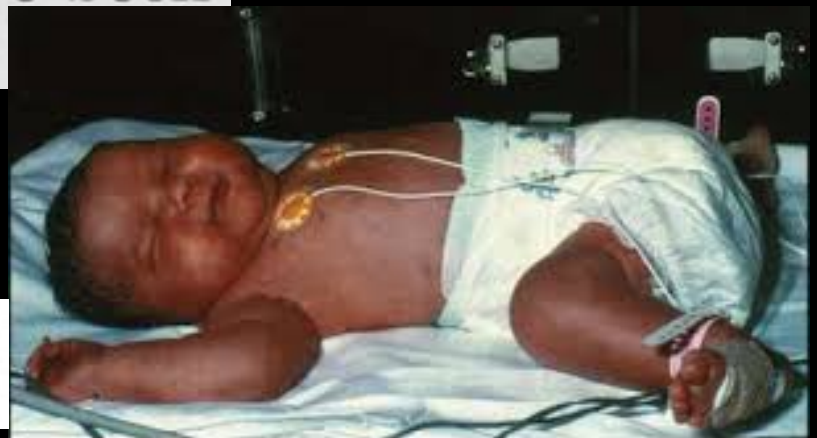

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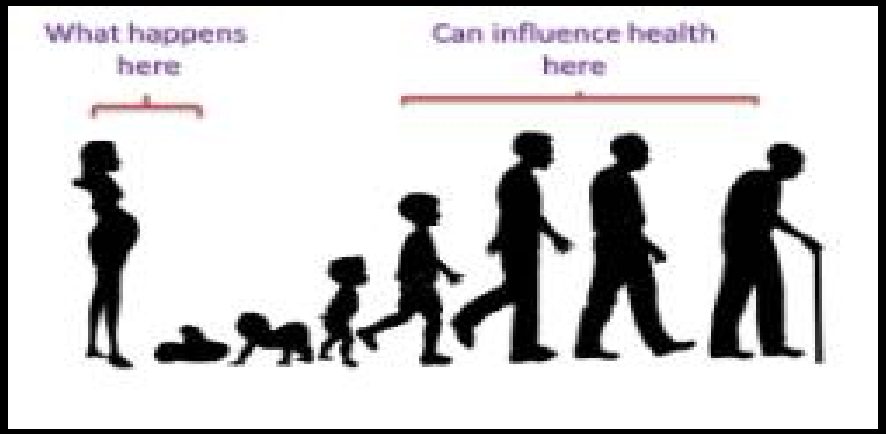
There is now robust evidence that a hyperglycemic intrauterine environment is responsible not only for significant short-term morbidity in the fetus and the neonate but also for an increased risk of developing diabetes as well as other chronic, noncommunicable diseases at adulthood



In the 1980s, David Barker and Colleagues proposed that the major causes of cardiovascular and metabolic diseases have their roots in early development

Mitanchez et sl . Best Practice & Research Clinical Obstetrics and Gynaecology (2015)

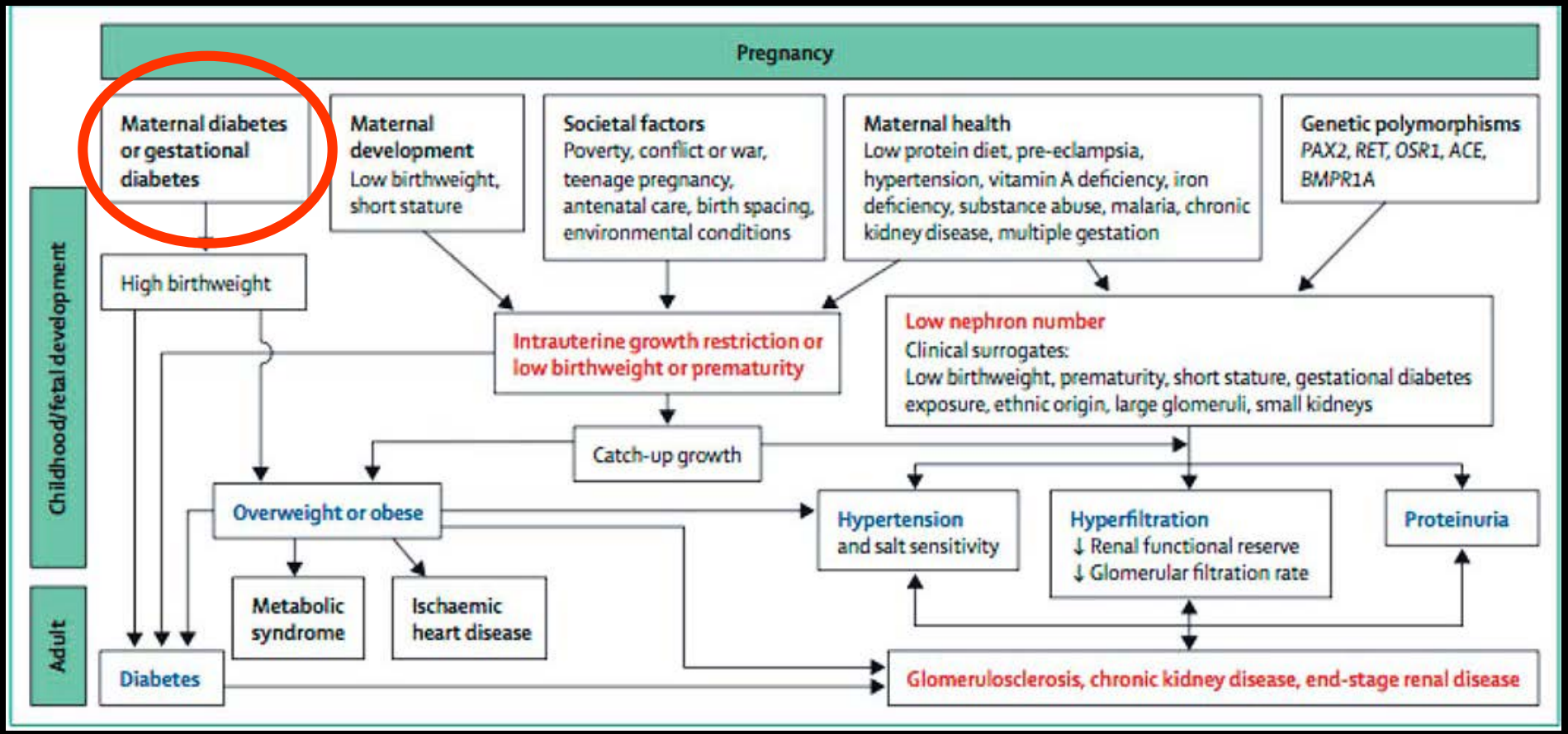
The Barker Hypothesis

Fetal Origins of Adult Disease

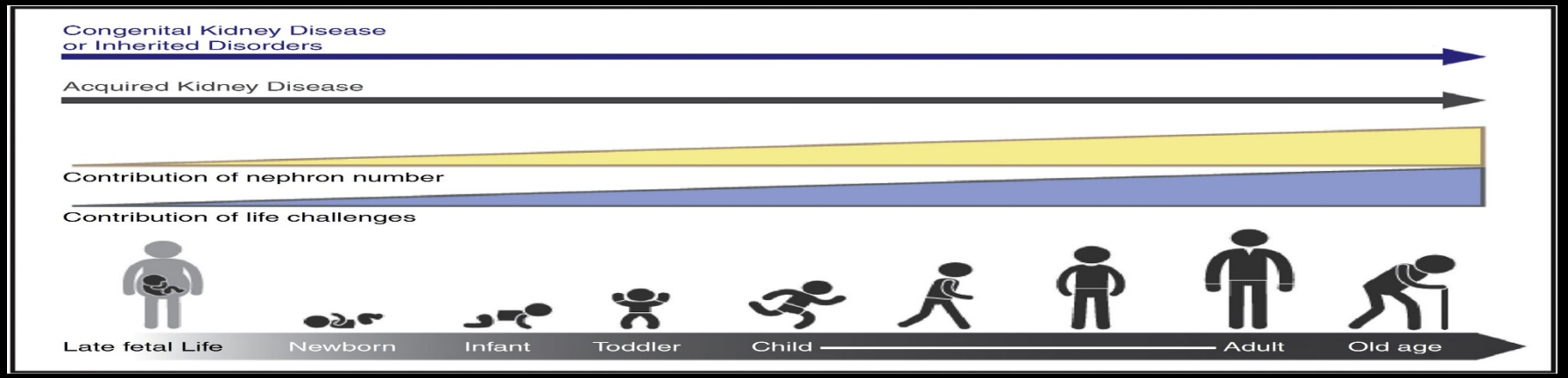
Adverse intrauterine events permanently "program" postnatal structure/function/homeostasis

"Adapted Birth Phenotype"

* Better chance of fetal survival
* Increased risk of adult disease



Nephron 2017;136:3–49



Original article

Diabetes in pregnancy and infant adiposity: systematic review and meta-analysis

Karen M Logan, Chris Gale, Matthew J Hyde, Shalini Santhakumaran, Neena Modi

What is already known on this topic?

- Offspring of mothers with diabetes have greater risks of adverse metabolic sequelae ir later life.
- The underlying mechanisms are unclear but increased infant adiposity is a plausible mediator.
- A strong association has been demonstrated between maternal glycaemia and infant adiposity using indirect (anthropometry-derived) techniques.

What this study adds?

- This study quantifies the overall difference in adiposity between infants of mothers with and without diabetes derived from all body composition techniques.
- Maternal diabetes is associated with higher fat mass, body fat % and skinfold thickness in infancy.
- In subgroup analyses of studies providing sex-specific data, adiposity was higher in infants of diabetic mothers compared with NIDM boys but not girls.

Logan KM, et al. Arch Dis Child Fetal Neonatal Ed 2017;102:F65–F72

Diabetes in Pregnancy: 2 Categories

Pregestational diabetes	Gestational diabetes
Pregnancy in pre-existing diabetes • Type 1 diabetes • Type 2 diabetes	Diabetes diagnosed in pregnancy

GDM
Gestational
Diabetes
Mellitus

GDM is associated with lower risks for maternal and neonatal complications compared with pregestational diabetes ;

the risk of cardiac malformations is increased for women with insulin-treated GDM, whereas the risk of nervous system malformations is not ;

the risk of respiratory distress is also increased for this subgroup of insulin-treated women with GDM;

Billionnet c et al. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012 *Diabetologia (2017)*

Table 6 Outcomes that were significantly increased in the insulin-treated GDM group

Outcome[a]	OR (95% CI)[b]
Delivery at >28 weeks	
Delivery at <37 weeks	1.2 (1.1, 1.2)
Caesarean section	1.4 (1.3, 1.4)
Macrosomia	1.3 (1.2, 1.4)
Cardiac malformation	1.4 (1.1, 1.7)
Delivery at ≥37 weeks	
Caesarean section	1.4 (1.3, 1.4)
Macrosomia	1.3 (1.2, 1.3)
Cardiac malformation	1.6 (1.2, 2.0)

Data excluded mothers to whom insulin or oral glucose-lowering agents were dispensed during the year after pregnancy

[a] Only outcomes with significant ORs ($p < 0.05$) are included

[b] Compared with the non-insulin-treated GDM group

Billionnet c et al. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012 *Diabetologia (2017)*

Practice points

Maternal diabetes during pregnancy should be screened and treated to improve neonatal outcomes.

Maternal obesity/overweight is an additional risk factor for adverse neonatal outcomes.

Pediatricians should be aware of the neonatal risks associated with diabetes in pregnancy

Mitanchez et sl . Best Practice & Research Clinical Obstetrics and Gynaecology (2015)

Intra-uterine exposure to maternal diabetes

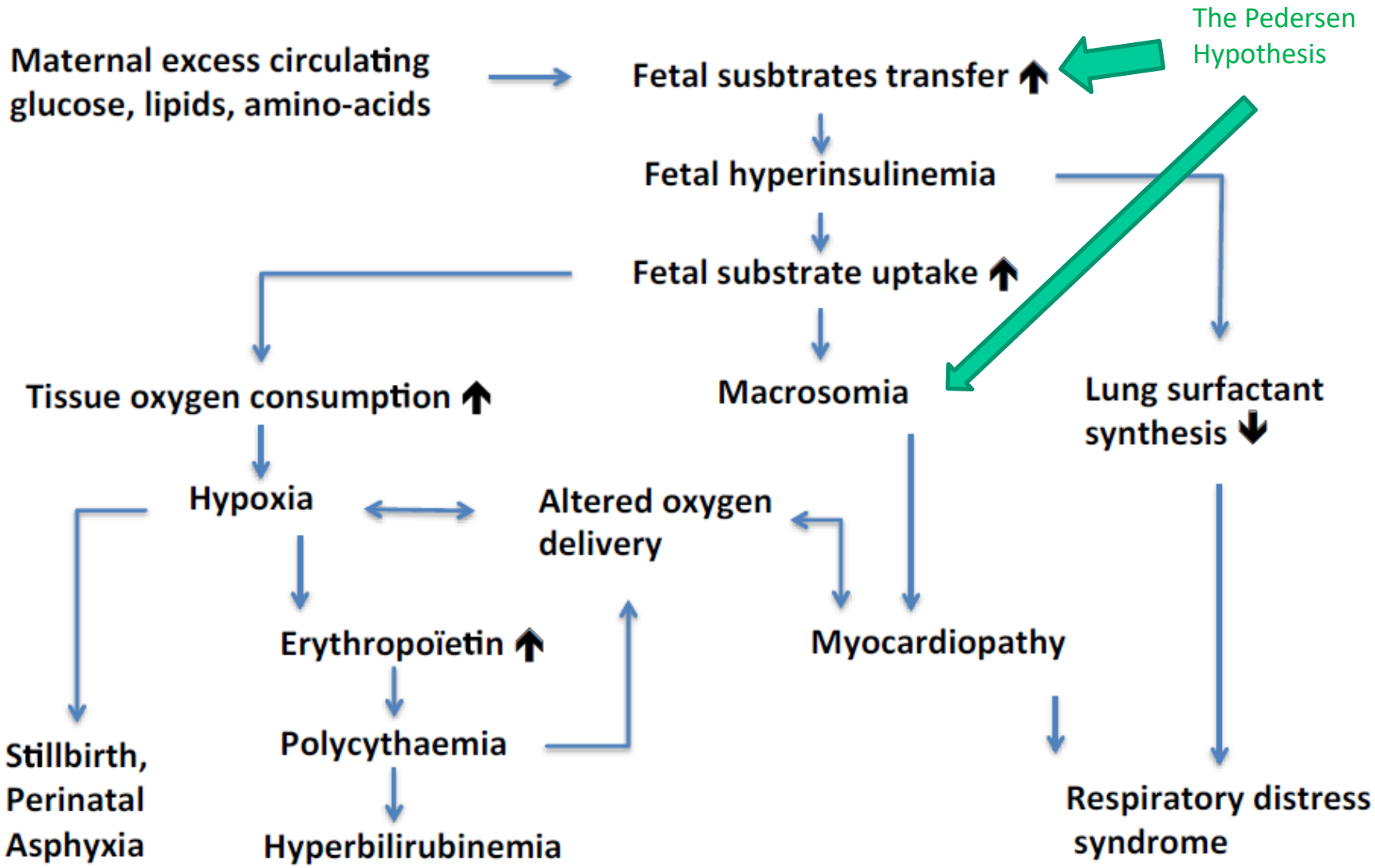


Fig. 1. Short-term complications of intrauterine exposure to maternal diabetes in the offspring.

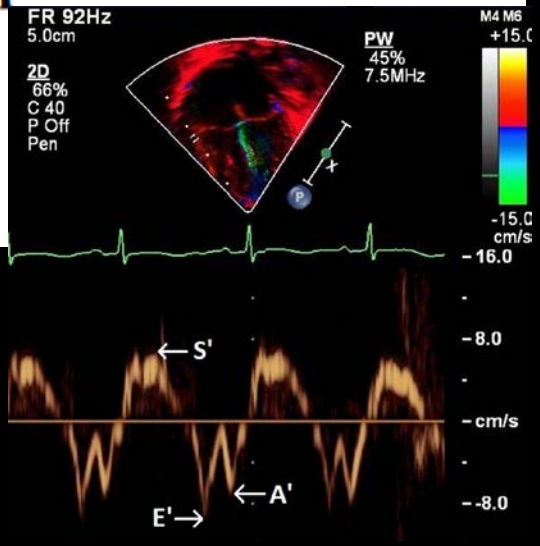
Mitanchez et sl . Best Practice & Research Clinical Obstetrics and Gynaecology (2015)

Pediatr Cardiol (2017) 38:801–806
DOI 10.1007/s00246-017-1584-y

ORIGINAL ARTICLE

Subclinical Decrease in Myocardial Function in Asymptomatic Infants of Diabetic Mothers: A Tissue Doppler Study

Jenny E. Zablah[1] · Dorota Gruber[1] · Guillaume Stoffels[2] · Estefania G. Cabezas[3] · Denise A. Hayes[1]



In asymptomatic newborn IDMs with normal two-dimensional echocardiographic evaluations, systolic and diastolic myocardial function (as assessed by pulsed wave TDI) is decreased compared to nIDMs. Our findings suggest that maternal diabetes mellitus is associated with inherent alterations in myocardial performance in neonates, even in the absence of ventricular hypertrophy.

Practice points

Maternal diabetes during pregnancy should be screened and treated to improve neonatal outcomes.

Maternal obesity/overweight is an additional risk factor for adverse neonatal outcomes.

Pediatricians should be aware of the neonatal risks associated with diabetes in pregnancy, especially RDS and hypoglycemia.

Mitanchez et sl . Best Practice & Research Clinical Obstetrics and Gynaecology (2015)

Annotation

Archives of Disease in Childhood, 1972, **47**, 679.

R. D. G. MILNER
Department of Child Health,
University of Manchester,
St. Mary's Hospital, Manchester 13 OJH.

Neonatal Hypoglycaemia—A Critical Reappraisal

HYPOGLYCEMIA AND BRAIN DEVELOPMENT

H. Peter Chase, M.D., Robert A. Marlow, B.A., Carol S. Dabiere, B.S., *and* N. Noreen Welch, B.A.

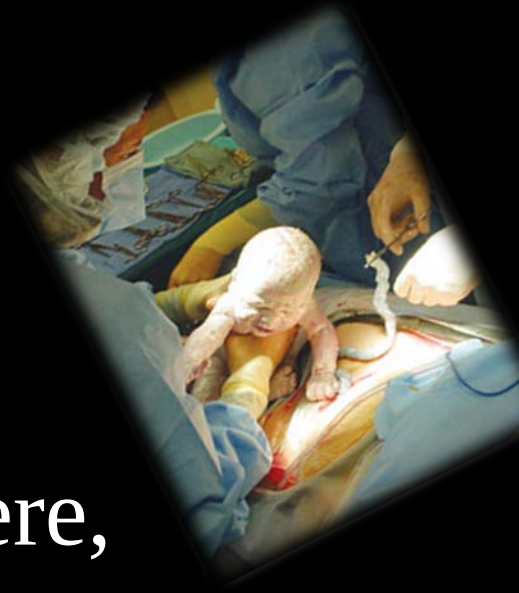
From the University of Colorado Medical Center, Denver, Colorado

Pediatrics,
52:513, 1973

ABSTRACT. Though hypoglycemia has been a common clinical condition known to affect human brain development, little has been done to define the resultant brain biochemical alterations. Because a controlled study of hypoglycemia in the newborn human infant is impossible, the infant rat was chosen as a model. Hypoglycemia induced once daily for 18 days following birth resulted in a generalized diminution of brain weight, cellularity, and protein content. The rate of formation of the myelin lipid sulfatide was decreased, as was the quantity of cerebroside-sulfatide in brains of hypoglycemic animals. Phospholipids, gangliosides, and cholesterol were decreased only in proportion to the decrease in brain weight. Brain glucose and glycogen concentrations were low in the brains of hypoglycemic animals, although ATP and phosphocreatine levels were not decreased. *Pediatrics*, 52:513, 1973, HYPOGLYCEMIA, BRAIN DEVELOPMENT, BRAIN DNA, BRAIN PROTEIN, BRAIN LIPIDS.

Despite more than 50 years of neonatal hypoglycaemia research, uncertainty remains about which newborns to screen, whether transient hypoglycaemia has untoward long term effects, and what concentration or range of glucose concentration should be used to define neonatal hypoglycaemia, as well as about management strategies and the incidence of transient hypoglycaemia

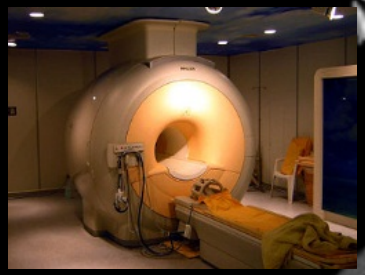
Jeffrey Kaiser et al. Association between transient newborn hypoglycemia and Fourth/Grade Achievement Test Proficiency. Jama Pediatr. 2015

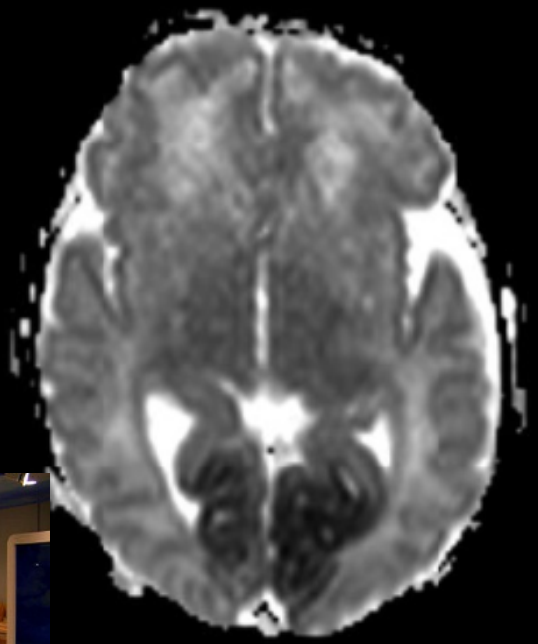


There is no doubt that severe, persistent hypoglycaemia can cause seizures and brain injury in newborns

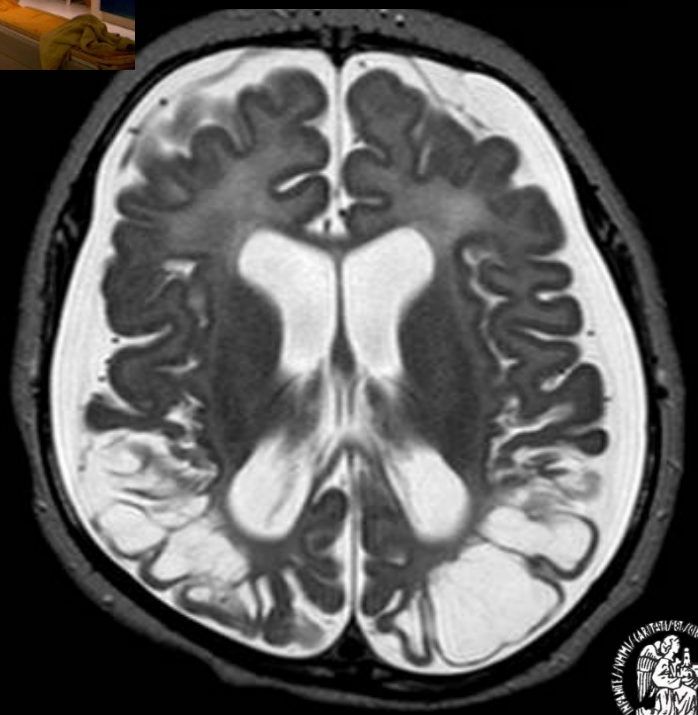
JaneHarding et al. An emerging evidence base for the management of neonatal hypoglycaemia Early Human Develop 2017

Some patients have a limited injury…





…Others have a more extensive damage with high risk of neurological and visual sequelae…



Nine developing focal occipital epilepsy and two developing a Lennox-Gastaut syndrome. Seizure outcome was favourable in later childhood or adolescence in six out of nine children with occipital epilepsy, but in neither of the two children with generalized epilepsy

What this paper adds

- Despite having bilateral occipital brain injury and neurological disability, six of the 11 children with epilepsy after neonatal hypoglycaemia had infrequent and potentially age-limited focal seizures.

Variable outcome for epilepsy after neonatal hypoglycaemia

CHOONG YI FONG.A SIMON HARVEY *DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY 2014*

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What this paper adds

- Despite having bilateral occipital brain injury and neurological disability, six of the 11 children with epilepsy after neonatal hypoglycaemia had infrequent and potentially age-limited focal seizures.

Many children with neonatal hypoglycaemia mild, focal epilepsy that may be ultimately age-limited, a point which has implications for counselling parents, choosing antiepileptic medications, and avoiding epilepsy surgery.

Variable outcome for epilepsy after neonatal hypoglycaemia

CHOONG YI FONG.A SIMON HARVEY *DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY 2014*

Occipital Lobe Injury and Cortical Visual Outcomes After Neonatal Hypoglycemia

Emily W. Y. Tam, MDCM[a], Elysa Widjaja, MD, FRCP[b], Susan I. Blaser, MD, FRCP(C)[b], Daune L. MacGregor, MD, FRCP(C)[a], Prakash Satodia, MD, FRCPCH[c], Aideen M. Moore, MD, FRCP(C), MHSc[d]

Department of Pediatrics, Divisions of [a]Neurology and [d]Neonatology, and [b]Department of Diagnostic Imaging, Division of Neuroradiology, Hospital for Sick Children, Toronto, Ontario, Canada; [c]Department of Pediatrics, Division of Neonatology, University Hospitals Coventry and Warwickshire National Health Service Trust, Coventry, England

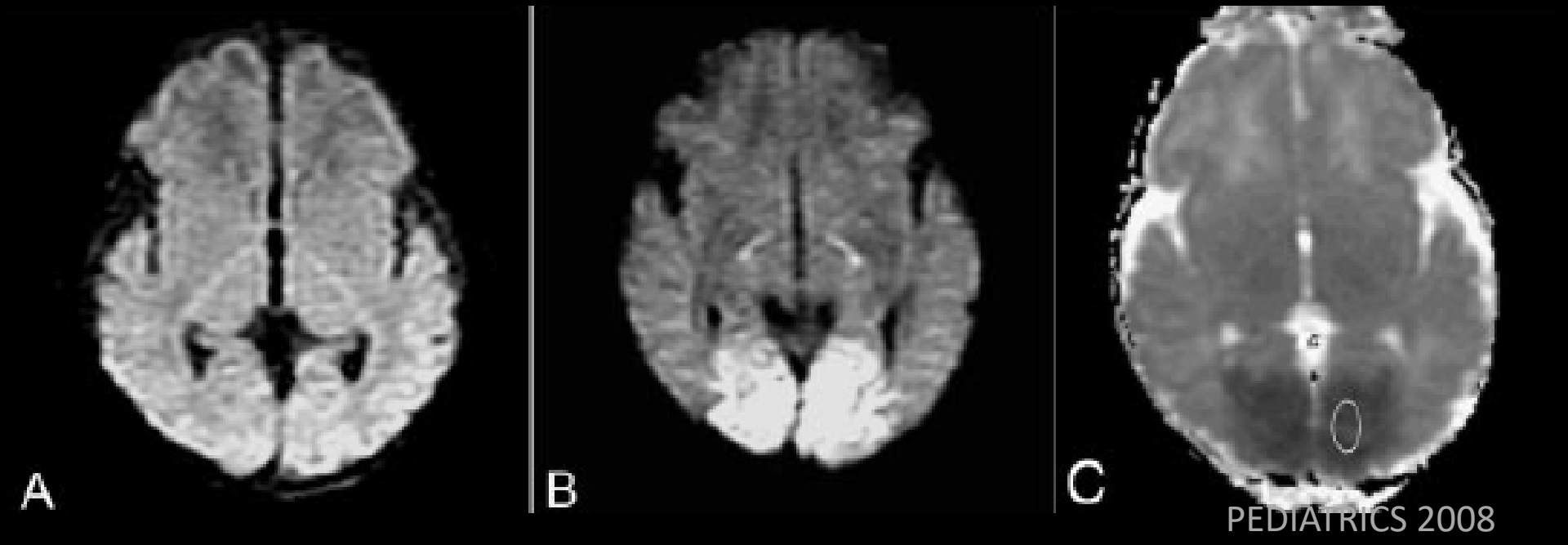
The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Short- and long-term neurologic effects, including optic nerve hypoplasia and visual deficits, after significant neonatal hypoglycemia have been reported. Recent neuroradiologic studies have shown occipitally predominant diffusion restriction associated with neonatal hypoglycemia.

TABLE 1 Demographic Data for Term and Preterm Subjects

	Term Neonates	Preterm Neonates
Gestational age at birth, median (range), wk	40.0 (37.0–41.0)	36.0 (35.0–36.9)
Birth weight, median (range), g	3117 (1940–5370)	2680 (1420–4185)
Lowest blood glucose level, median (range), mmol/L	1.2 (0–2.1)	0.8 (0–2.1)
Time with hypoglycemia, median (range), d	2 (1–6)	1 (1–8)



PEDIATRICS 2008

Diffusion-weighted imaging studies performed within 6 days after initial hypoglycemia were sensitive in term but not preterm neonates. Diffusion restriction, with low apparent diffusion coefficient values, in the mesial occipital poles may indicate the prognosis for visual outcomes in acute settings after neonatal hypoglycemia

cortical visual loss was documented for 6 (33%) of 18 infants with hypoglycemia measured on 2 days. No infants with hypoglycemia documented on a single day showed long-term visual loss

PEDIATRICS 2008

American Academy of Pediatrics

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The American College of Obstetricians and Gynecologists

WOMEN'S HEALTH CARE PHYSICIANS

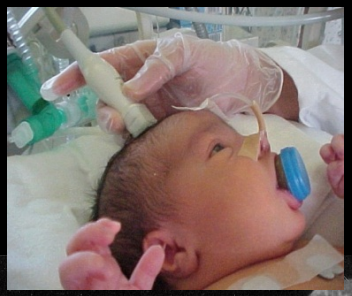
Neonatal Encephalopathy

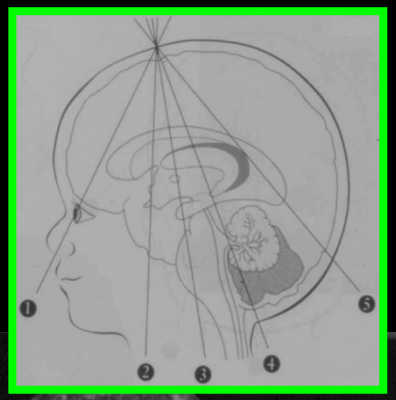
Clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes.

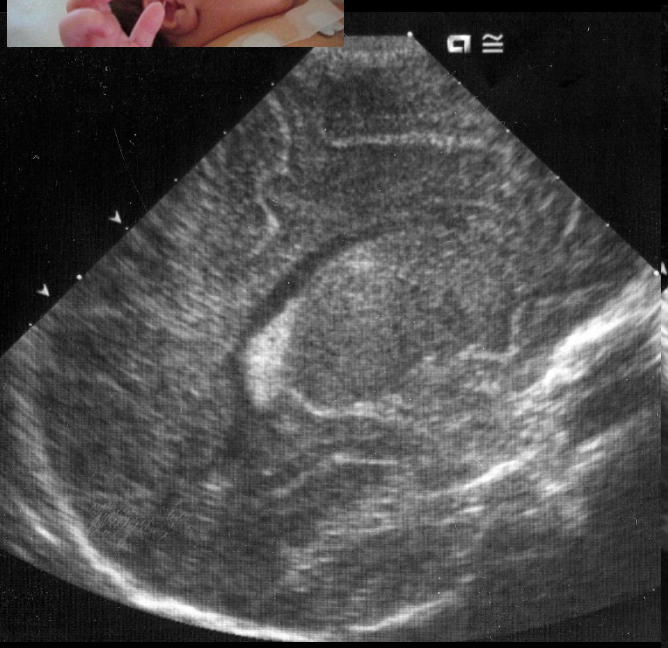
PEDIATRICS Volume 133, Number 5, May 2014

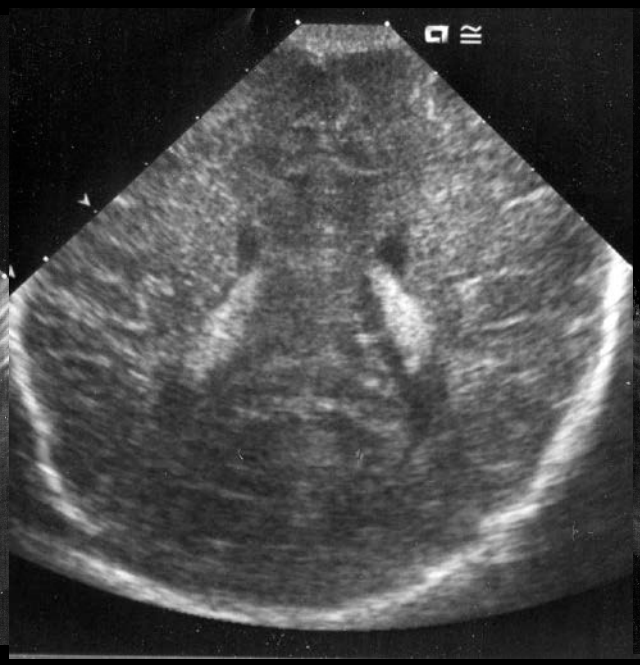
35 wks, US at 48 hrs
1 hour after severe apnea
Severe hypoglycaemia (4 mg / dl !!)

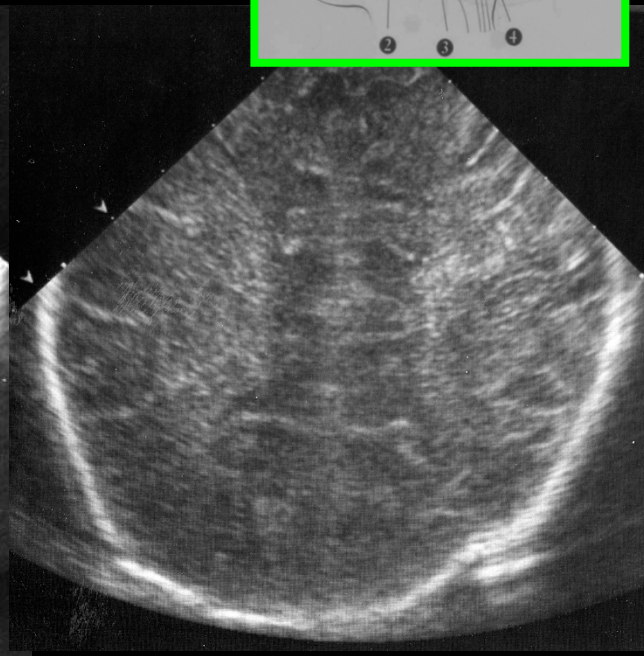
No clear fits but " hypotonic and later flat"
Resuscitated , abnormal EEG









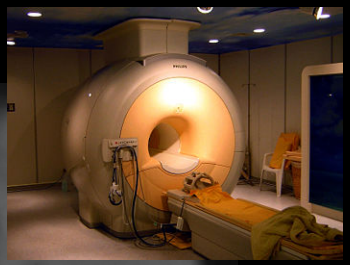


Mangiagalli (Milan) data

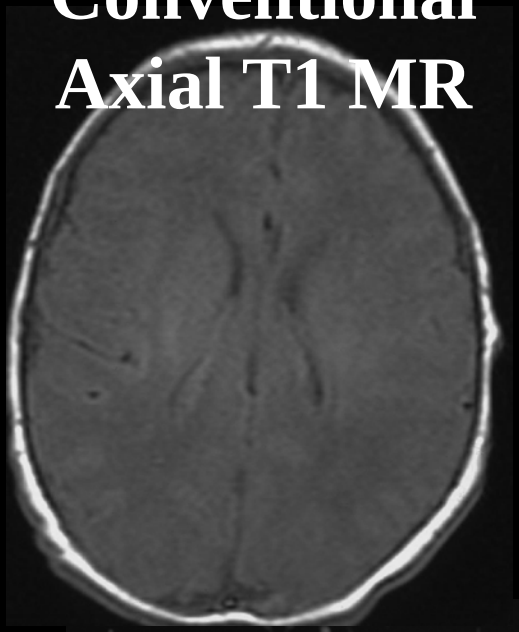
Conventional Axial T1 MR

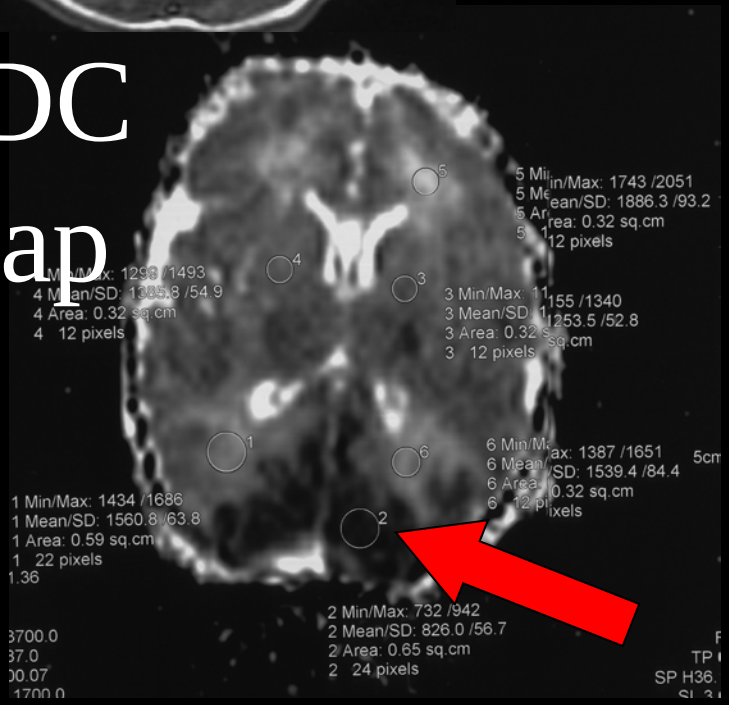
MR 2 hrs after Hypoglycaemia

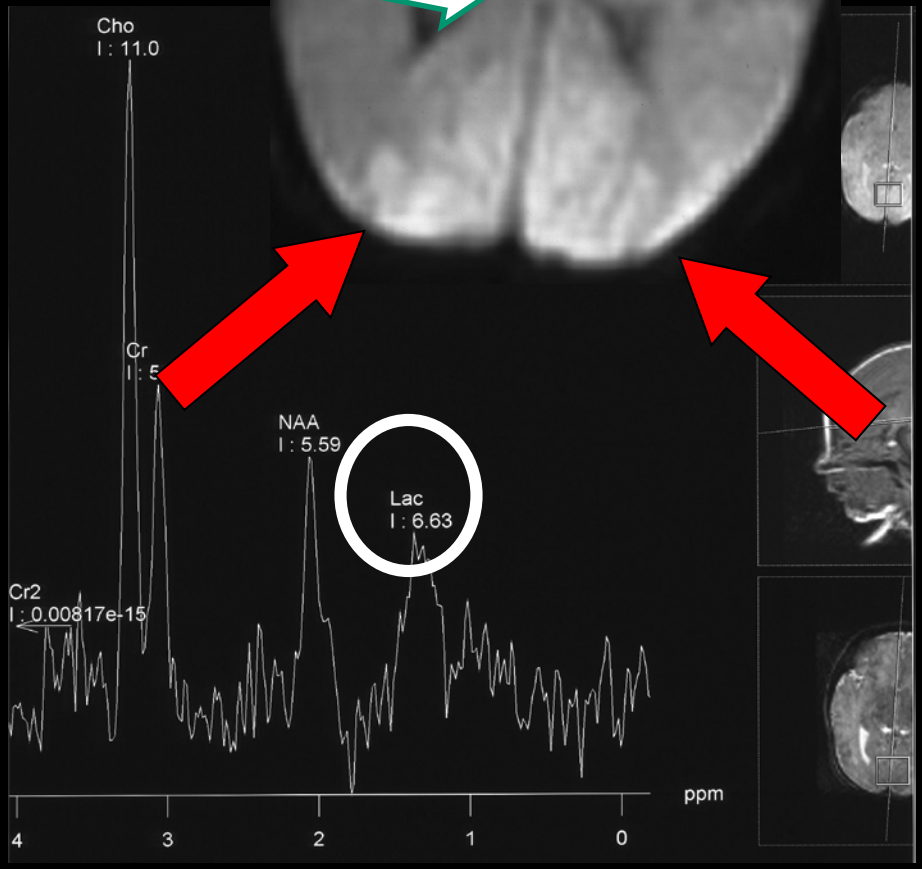
DWI



ADC map



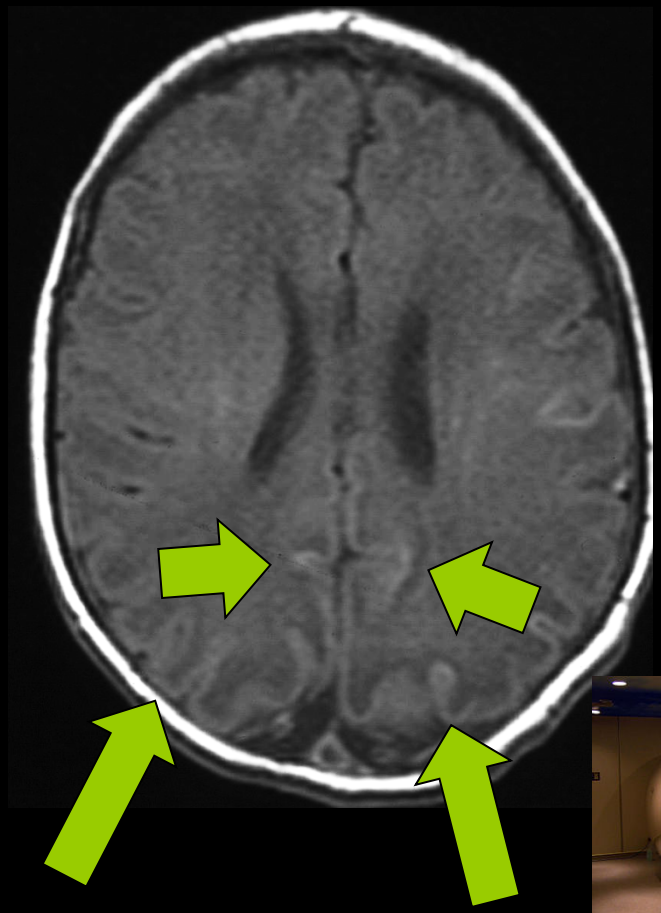


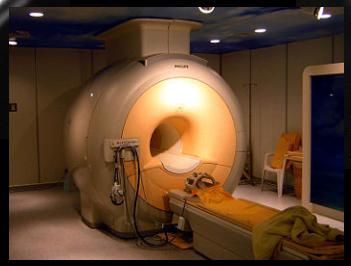


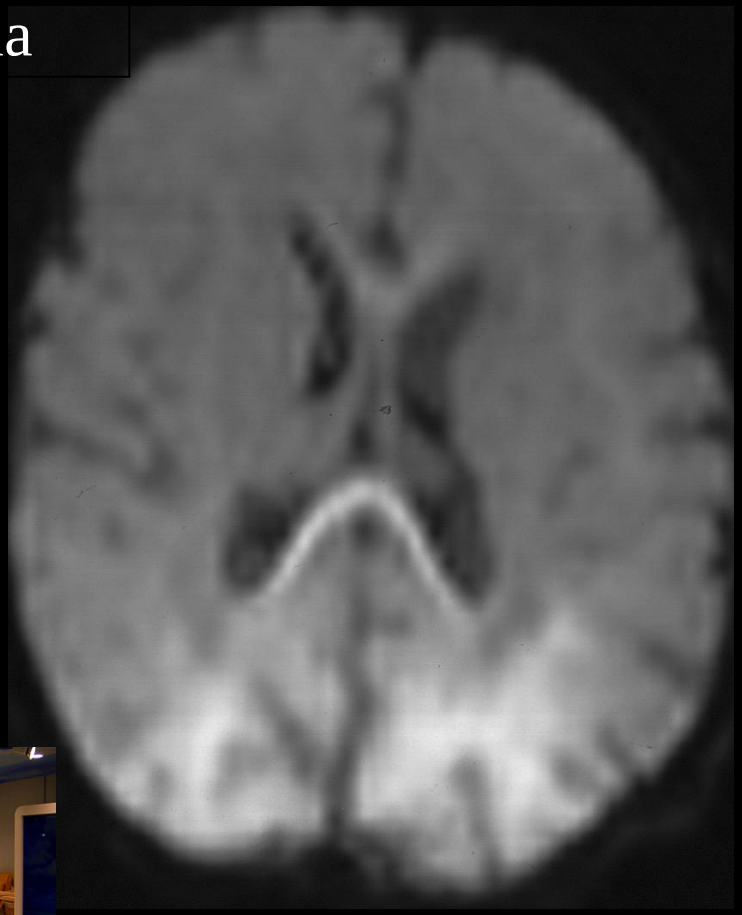
Axial T1

Policitemia
Ipoglicemia

DWI







After one week …. Still DWI anomaly, more obvious

T1 weighted starts to be abnormal

T 2
at day 5

ADC
at day

- Movimenti non coniugati
- ↓ campi visivi a destra
- iperfissazione

Ricci et, "Early assessment of visual function in full term newborns", 2007

AD
Afte

FH 1

FH 1

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WOMEN'S HEALTH CARE PHYSICIANS

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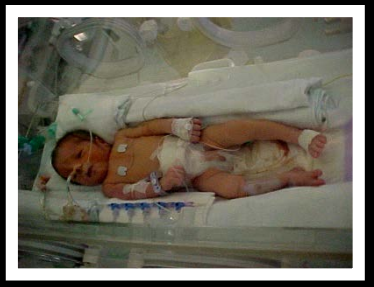
PEDIATRICS Volume 133, Number 5, May 2014

Neonatal Encephalopathy

Asphyxia

Encephalopathyc Neonate

Early neonatal seizures



Low Apgar scores

↓

Aphyxia (Hypoxic-ischaemic encephalopathy” HIE)

Normal Apgar scores

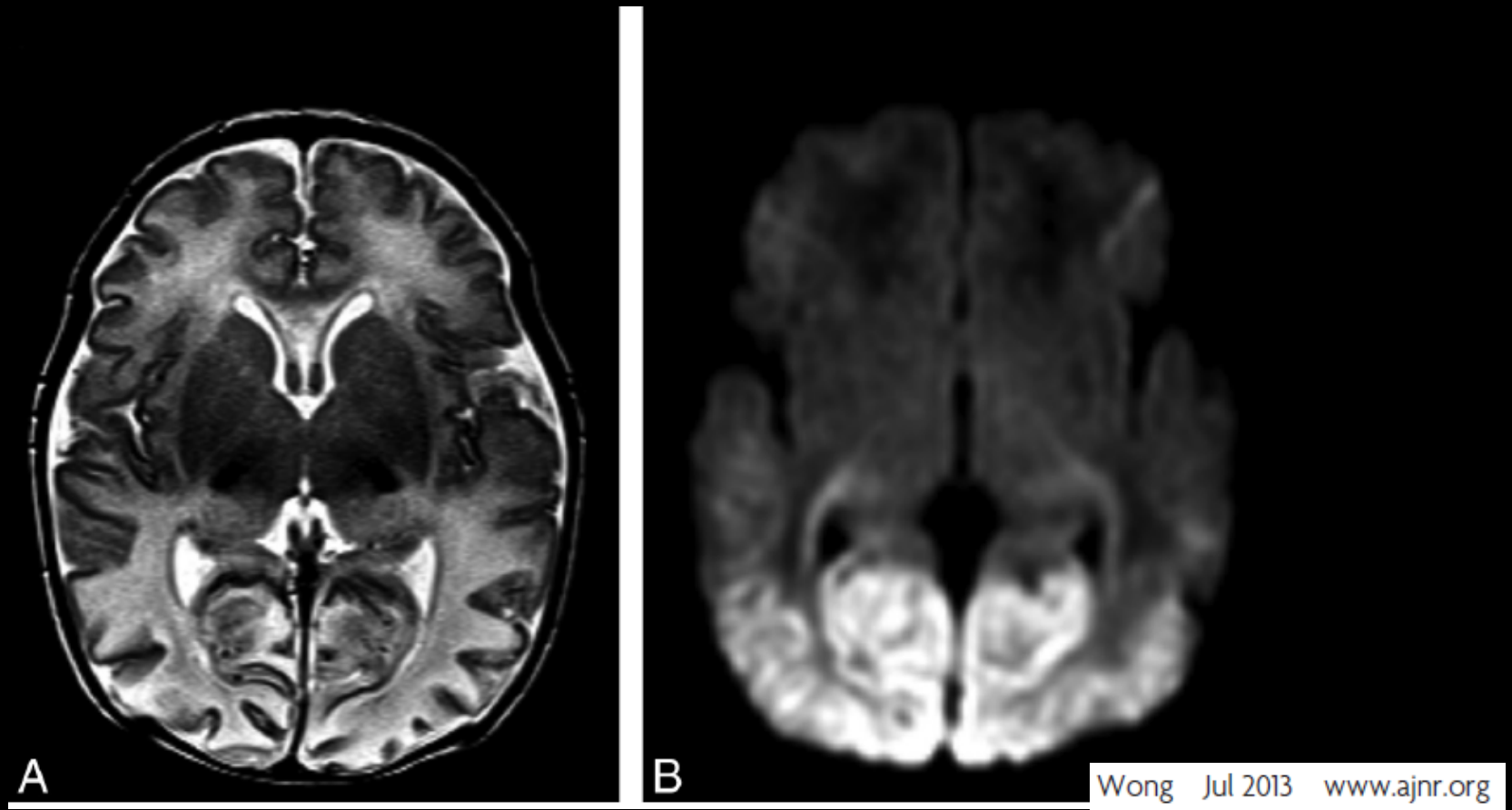
↓

ischaemic
haemorrhagic
infection
hypoglycaemia
hyperbilirubinaemia
neurometabolic
neuronal migration

ORIGINAL RESEARCH
PEDIATRICS

Brain Injury Patterns in Hypoglycemia in Neonatal Encephalopathy

D.S.T. Wong, K.J. Poskitt, V. Chau, S.P. Miller, E. Roland, A. Hill, and E.W.Y. Tam



Contribution of the blood glucose level in perinatal asphyxia.

Basu P. Et al. Eur J Pediatr (2009) 168:833–838

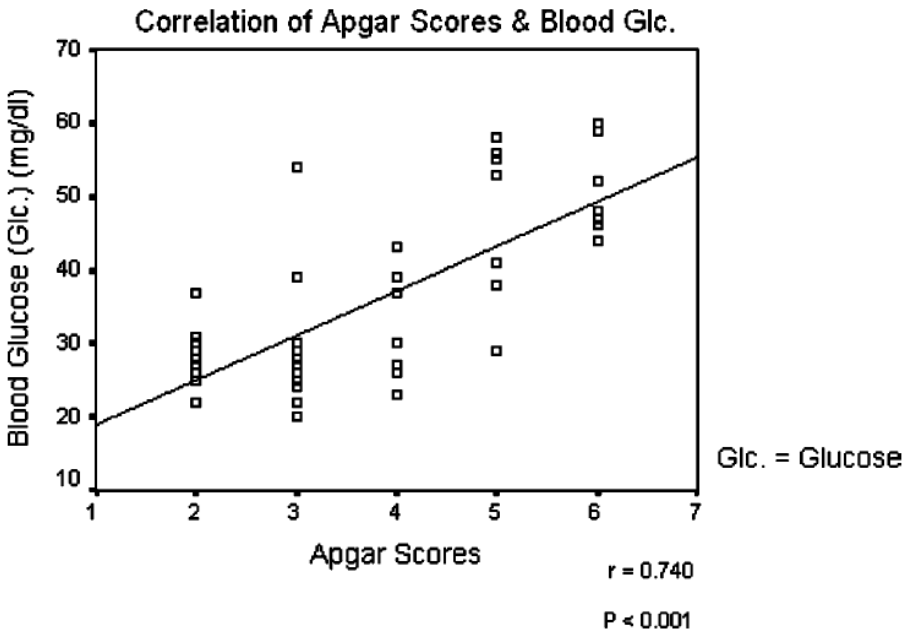


Fig. 2 Linear regression analysis shows the correlation between Apgar score and the blood glucose level in asphyxiated babies. r=0.740, P<0.001

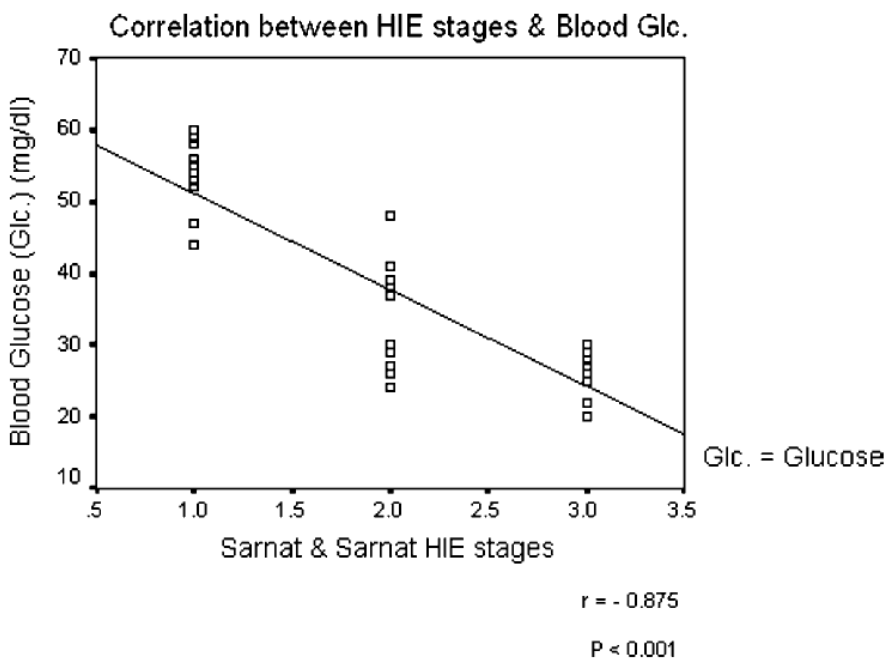
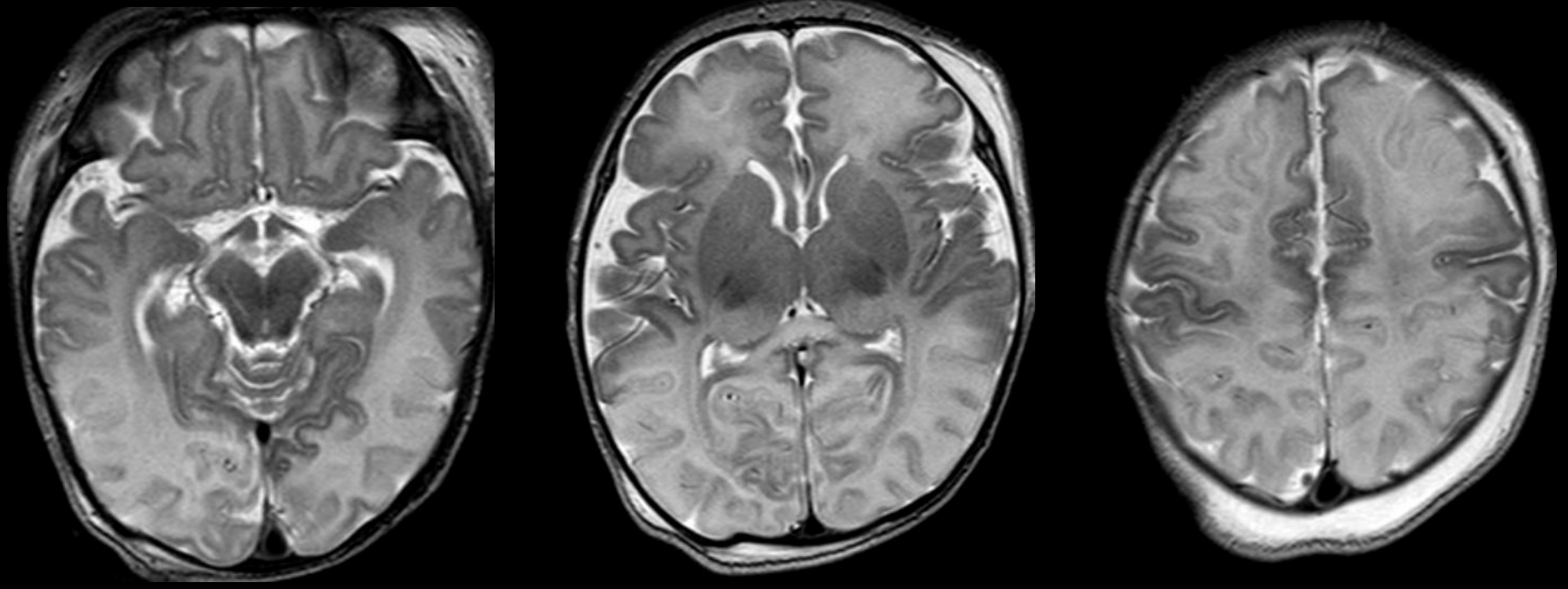
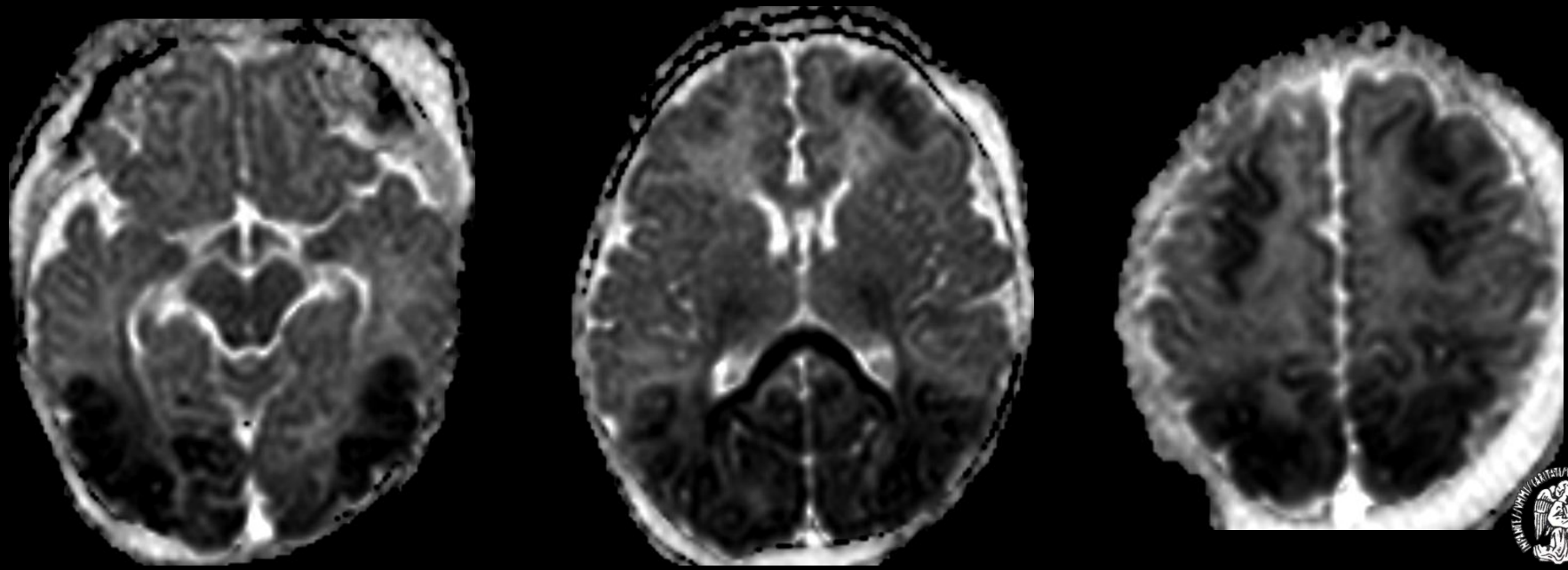


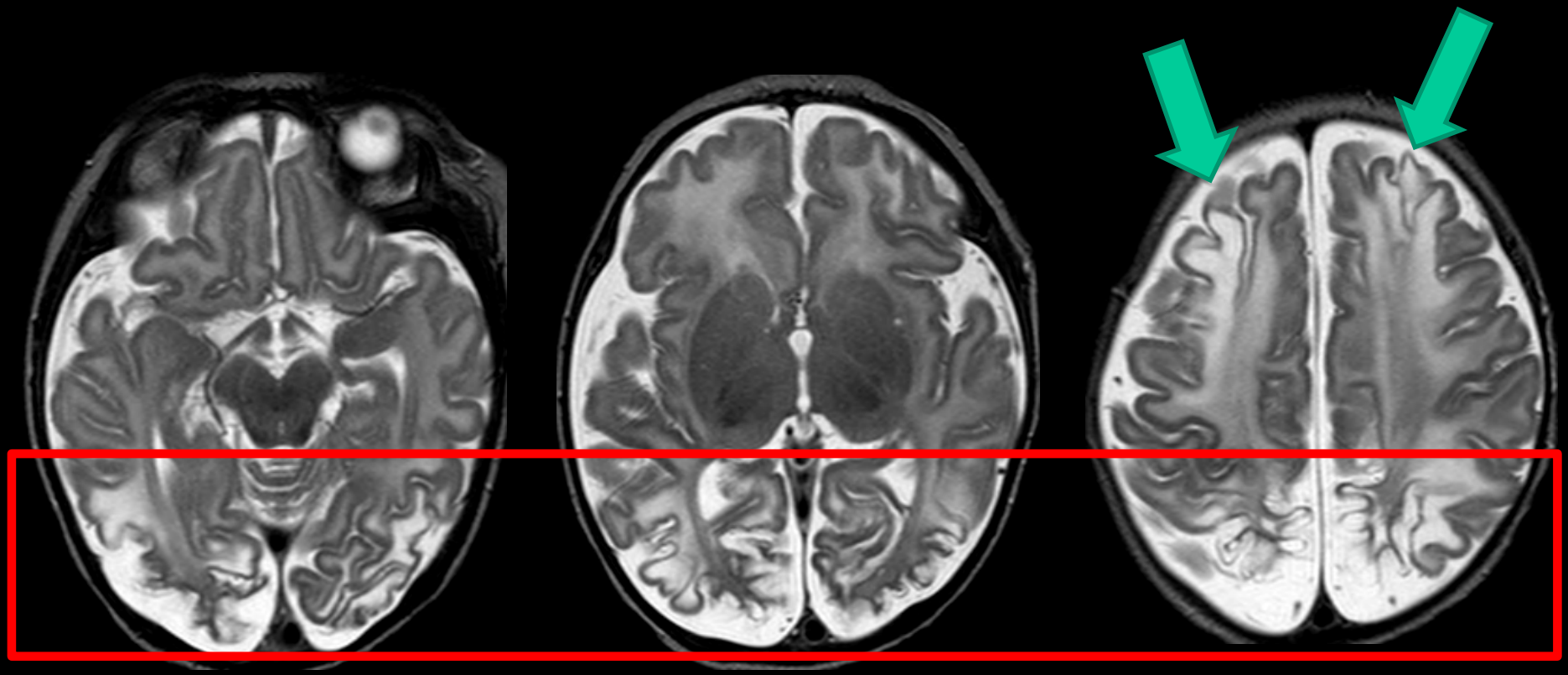
Fig. 3 Linear regression analysis shows the correlation between hypoxic ischemic encephalopathy (HIE) stages and the blood glucose level in asphyxiated babies. r=−0.875, P<0.001



MRI after cooling (day 5): hypoglycaemia?



Day 21



Hypoglycaemia + asphyxia

Wong DS, AJNR 2013

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

The American College of Obstetricians and Gynecologists

WOMEN'S HEALTH CARE PHYSICIANS

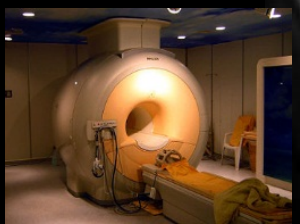
Neonatal Encephalopathy

Clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes.

PEDIATRICS Volume 133, Number 5, May 2014

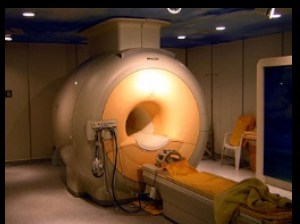
DWI

ADC



T1

T2



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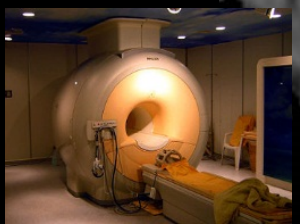
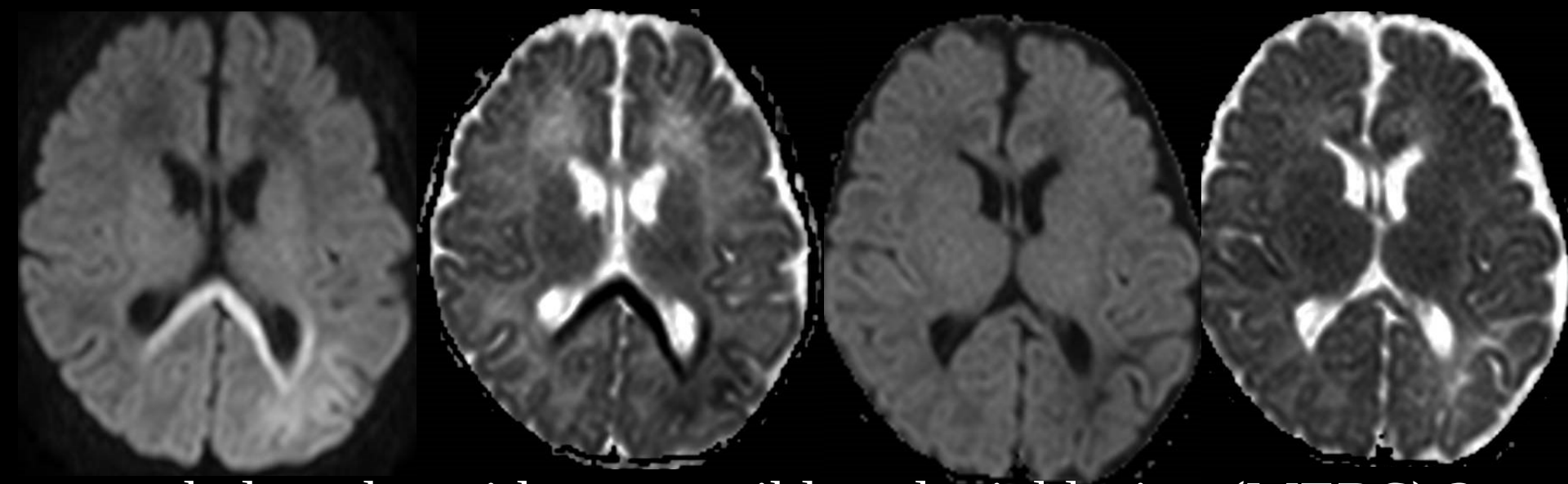
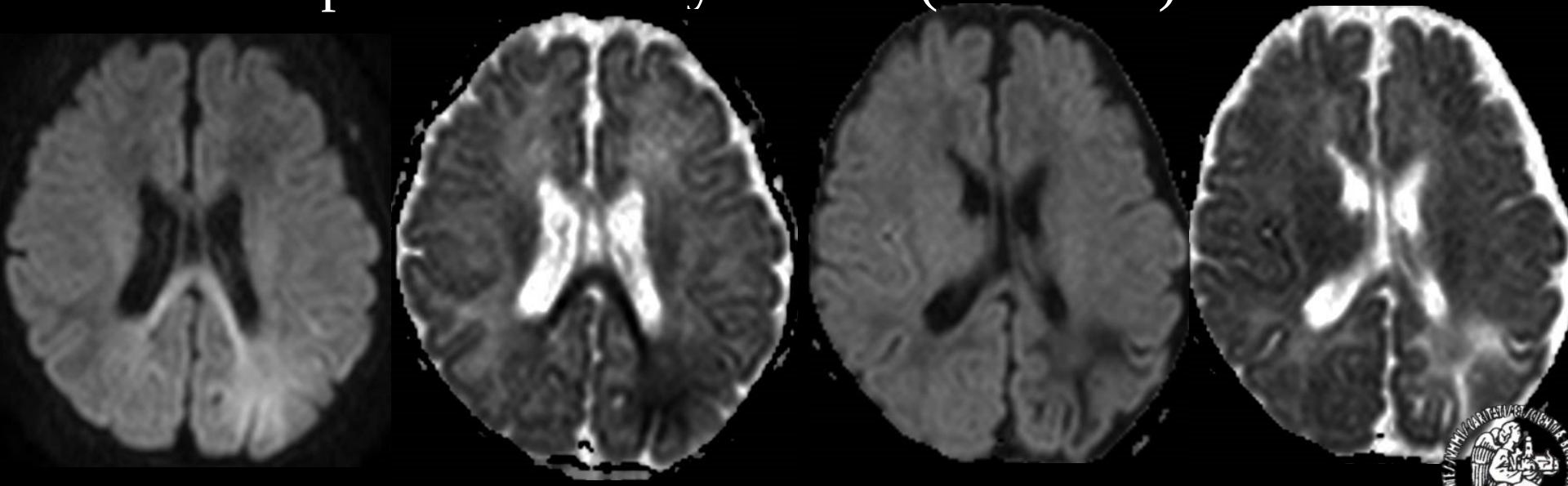




encephalopathy with a reversible splenial lesion (MERS) ?

reversible splenial lesion syndrome (RESLES) ?

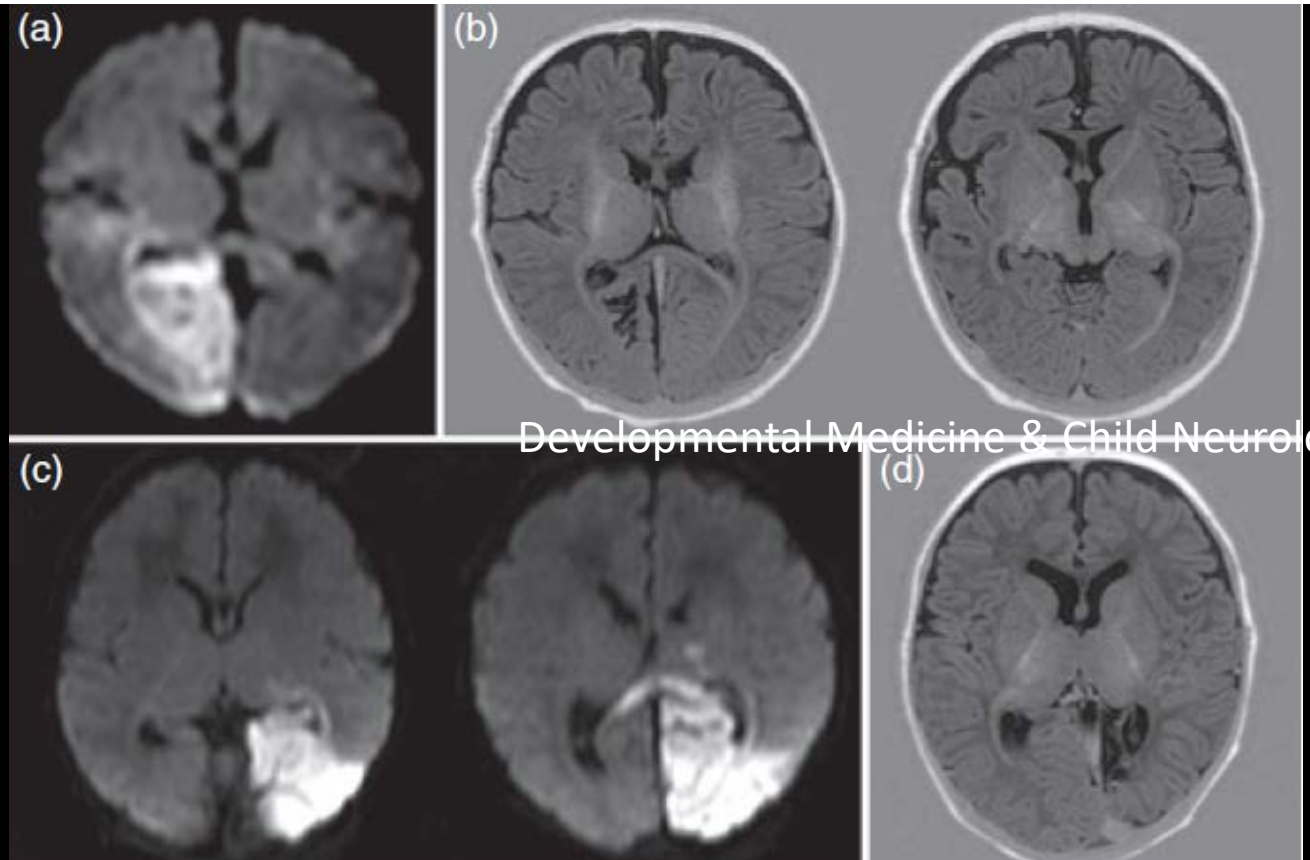


DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Neonatal posterior cerebral artery stroke: clinical presentation, MRI findings, and outcome

NIEK E VAN DER AA[1] | JEROEN DUDINK[2,3] | MANON J N L BENDERS[1] | PAUL GOVAERT[2] | HENRICA L M VAN STRAATEN[4] | GIORGIO L PORRO[5] | FLORIS GROENENDAAL[1] | LINDA S DE VRIES[1]

1 Department of Neonatology, Wilhelmina Children's Hospital, Utrecht; **2** Department of Neonatology, Sophia Children's Hospital, Rotterdam; **3** Department of Radiology, Erasmus Medical Centre, Rotterdam; **4** Department of Neonatology, Isala Clinics, Zwolle; **5** Department of Ophthalmology, University Medical Centre Utrecht, Utrecht, the Netherlands.



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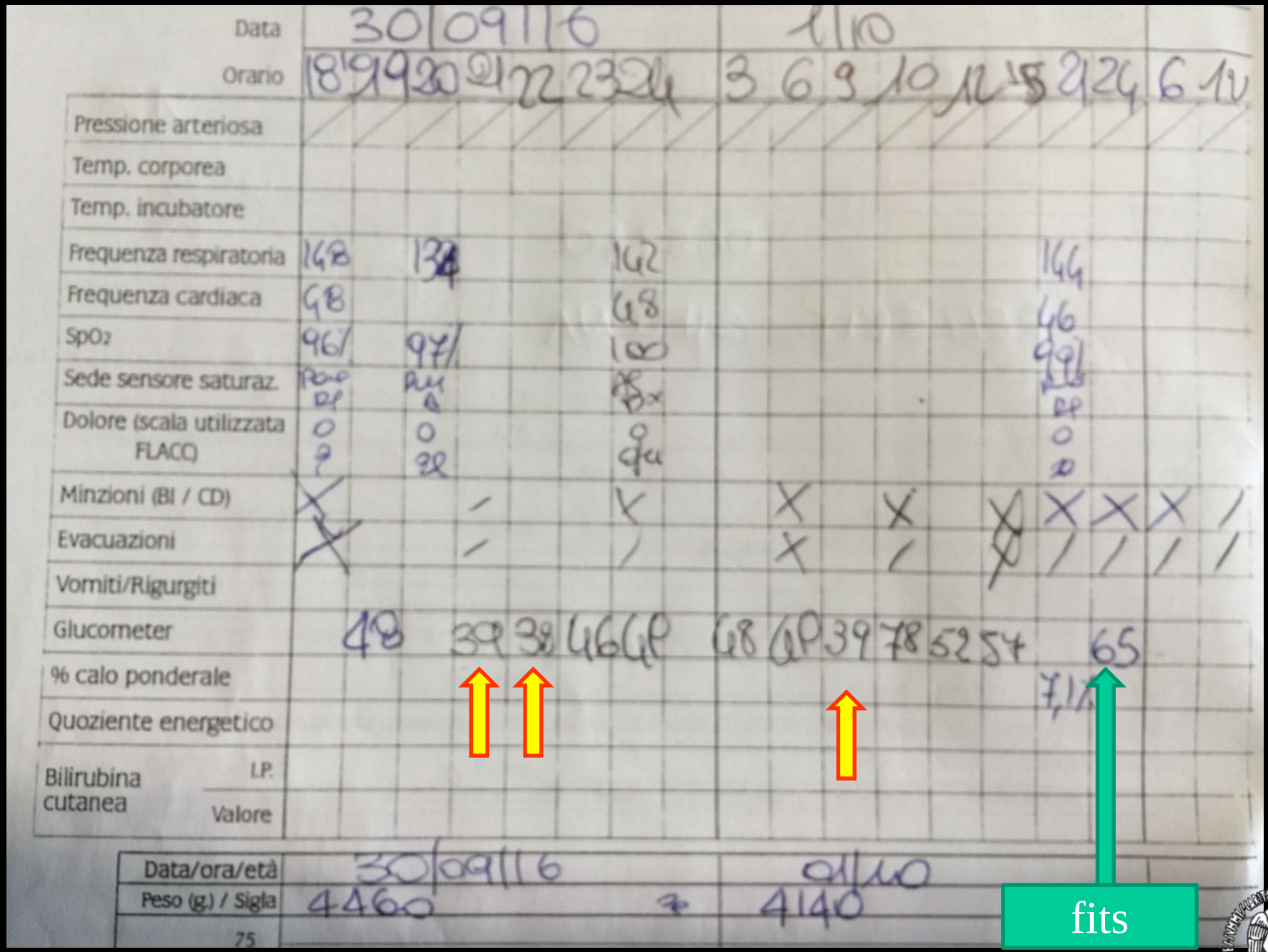
The clinical presentation of newborn infants, diagnosed with PAIS in the PCA territory, varies and often involves clinical seizures. Although many newborn infants were diagnosed with hypoglycaemia, its exact role in the pathogenesis of PCA stroke requires further investigation. Despite the overall good long-term neurodevelopmental outcome, follow-up of these infants is required, as development of a visual field is frequently observed.


Data
30/09/16
1/10
Orario
18 19 20 21 22 23 24 3 6 9 10 12 15 21 24 6 12
Pressione arteriosa
Temp. corporea
Temp. incubatore
Frequenza respiratoria
168 134 162 144
Frequenza cardiaca
98 98 96
SpO2
96 97 100 99
Sede sensore saturaz.
Dolore (scala utilizzata FLACC)
Minzioni (BI / CD)
Evacuazioni
Vomiti/Rigurgiti
Glucometer
48 39 38 46 68 39 78 52 54 65
% calo ponderale
7,1
Quoziente energetico
Bilirubina cutanea
LP.
Valore
Data/ora/età
30/09/16
01/10
Peso (g.) / Sigla
4460
4140
75
fits

?

Neonatal hypoglycemia is common and can cause neurologic impairment, but evidence supporting thresholds for intervention is limited.

Christopher J.D. McKinlay, Ph.D et al.
Neonatal Glycemia and Neurodevelopmental Outcomes at 2 years. *N Engl J Med*. 2015

Eligible infants were those at risk for neonatal hypoglycemia primarily on the basis of maternal diabetes, preterm birth (gestational age of <37 weeks), or a birth weight that was low (<10th percentile or <2500 g) or high (>90th percentile or >4500 g).

Hypoglycemia, defined as a blood glucose concentration of less than 47 mg per deciliter (2.6 mmol per liter), was treated with any combination of additional feeding, buccal dextrose gel, and intravenous dextrose to maintain a blood glucose concentration of at least 47 mg per deciliter

Christopher J.D. McKinlay, Ph.D et al.
Neonatal Glycemia and Neurodevelopmental Outcomes at 2 years. *N Engl J Med*. 2015

RESULTS

we found that with a treatment threshold of 47 mg of glucose per deciliter, neonatal hypoglycemia was not associated with adverse neurodevelopmental outcomes at 2 years.

a protocol of regular blood glucose monitoring in the first 48 hours after birth and intervention aimed at maintaining a blood glucose concentration of at least 47 mg per deciliter is effective in preventing neuronal injury in at-risk term and late-preterm newborns.

Christopher J.D. McKinlay, Ph.D et al.
Neonatal Glycemia and Neurodevelopmental Outcomes at 2 years. *N Engl J Med*. 2015

It is important to distinguish between thresholds for intervention that can be safely applied to all infants and the lowest glucose concentration at which clinically significant neuroglycopenia is avoided. It is unlikely that neuroglycopenia can be defined by a single numerical value, since the relationships among glycemic exposure, alternative cerebral fuels, other perinatal stressors, and neuronal function are complex and may be highly infant-specific.

Christopher J.D. McKinlay, Ph.D et al.
Neonatal Glycemia and Neurodevelopmental Outcomes at 2 years. *N Engl J Med*. 2015

A surprising finding of our study is the association of neurosensory impairment, especially cognitive delay, with higher glucose concentrations and less glucose stability, indicated by a larger proportion of time outside the central range of 54 to 72 mg per deciliter in the first 48 hours.

Of concern that rapid correction of hypoglycemia to higher blood glucose concentrations may be associated with a poorer outcome

Christopher J.D. McKinlay, Ph.D et al.
Neonatal Glycemia and Neurodevelopmental Outcomes at 2 years. *N Engl J Med*. 2015

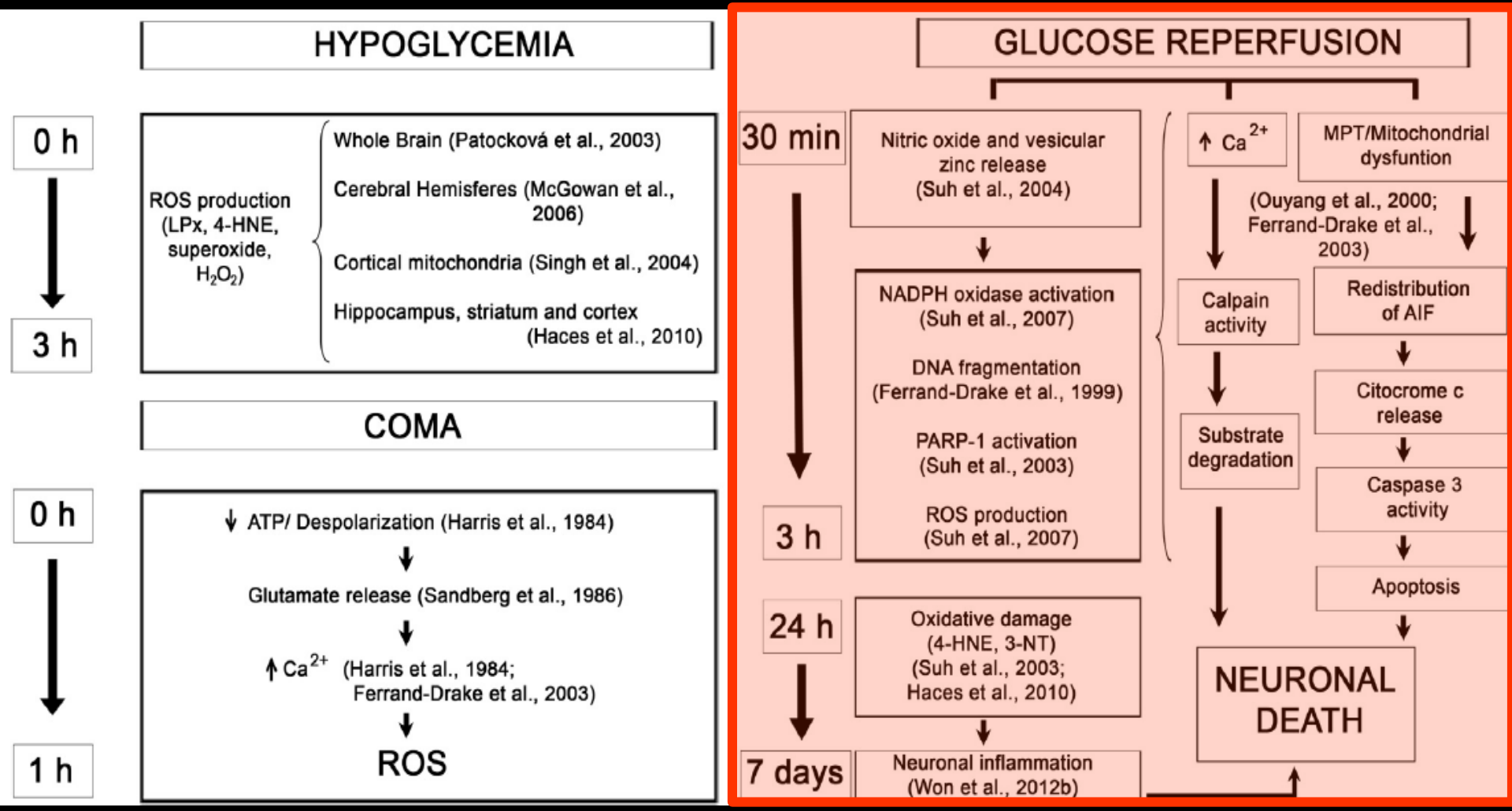


Fig. 1. Factors involved in neuronal death associated with severe hypoglycemia and their time-course of occurrence. Reactive Oxygen Species (ROS), Poly-(ADP ribose) polymerase-1 (PARP-1), Mitochondrial permeability transition pore (MPT), Nitric Oxide Synthase (NOX), 3-Nitrotyrosine (3-NT), 4-Hydroxinonenal (4-HNE), Lipid peroxidation (LPx), Apoptosis Inducing Factor (AIF).

Gabriela Languren et al. *Neuronal damage and cognitive impairment associated with hypoglycemia: An integrated view*. Neurochemistry International (2013)

A surprising finding of our study is the association of neurosensory impairment, especially cognitive delay, with higher glucose concentrations and less glucose stability, indicated by a larger proportion of time outside the central range of 54 to 72 mg per deciliter in the first 48 hours.

Of concern that rapid correction of hypoglycemia to higher blood glucose concentrations may be associated with a poorer outcome

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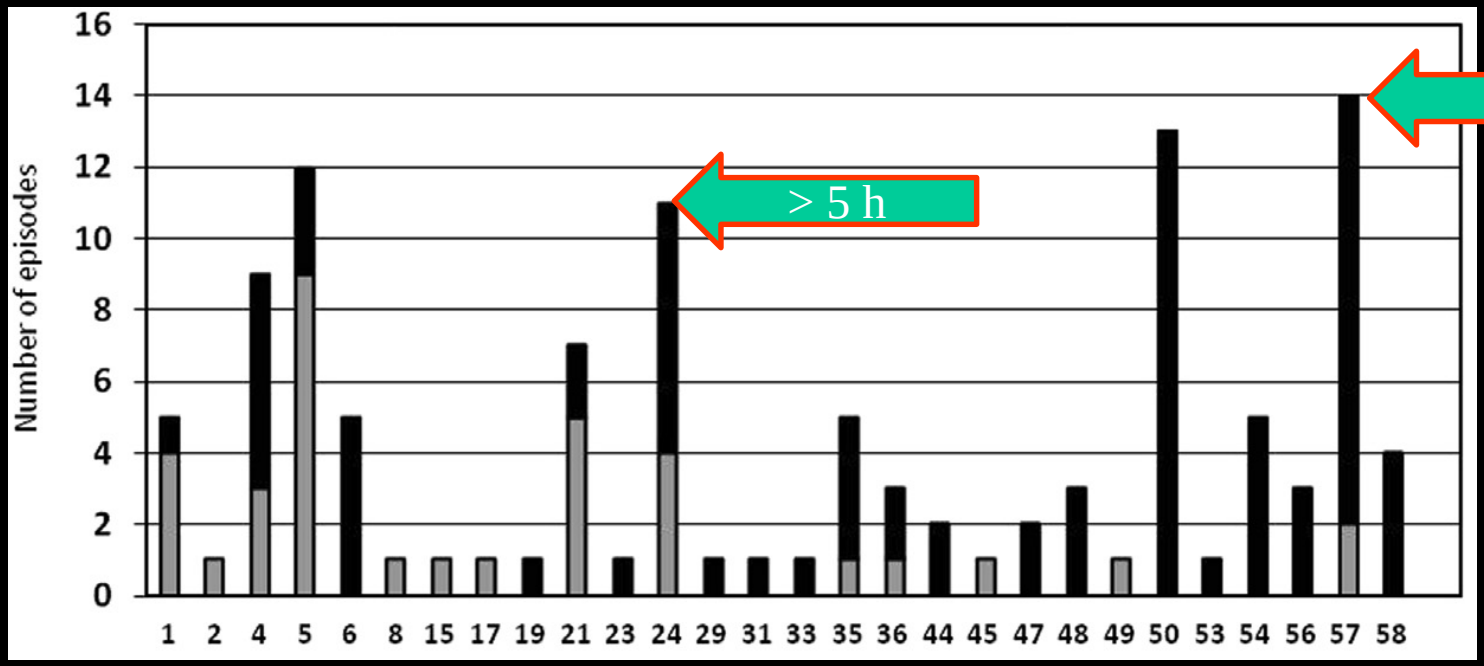
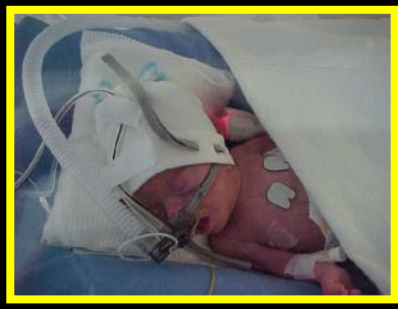
Neonatal Glycemia and Neurodevelopmental Outcomes at 2 years. *N Engl J Med*. 2015

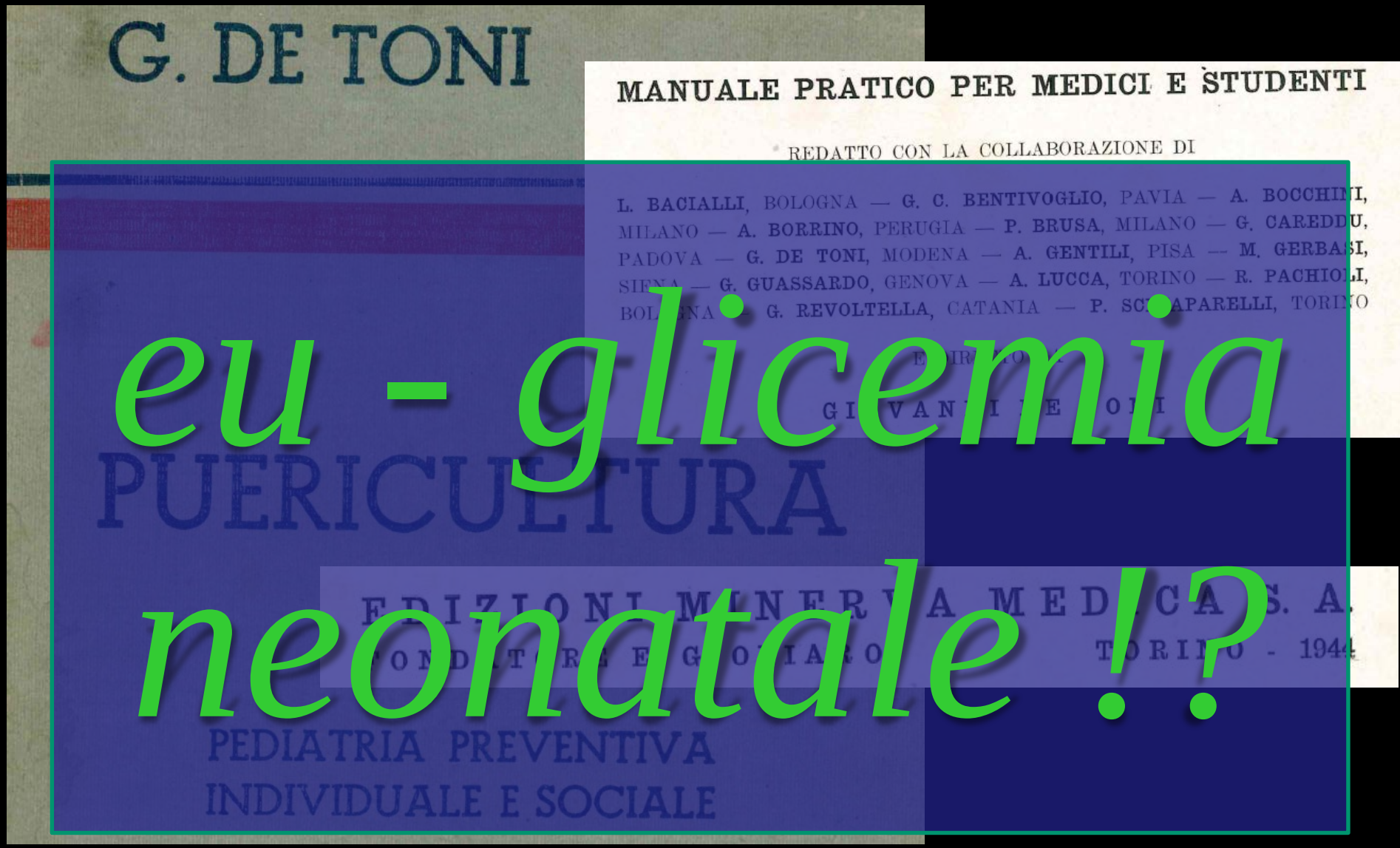
Glucose levels were intermittently or continuously monitored during 48 hours in a cohort of 60 VPT infants near hospital discharge. Hypoglycemic (45 mg/dL, 2.5 mmol/L) and hyperglycemic (140 mg/dL or 7.8 mmol/L, severe if 180 mg/dL or 10mmol/L) episodes were considered relevant if they lasted longer than 30 minutes.



Number of episodes of abnormal glucose per patient



Africa Pertierra-Cortada et al. **Instability of Glucose Values in Very Preterm Babies at Term Postmenstrual Age**. J.Pediatr 2014,



eu - glicemia neonatale !?

Breast-feeding

Must be encouraged and started as soon as possible after birth in infants born to diabetic mothers.

Reduces the risk of later obesity and decreases childhood adiposity and slows growth velocity during infancy.

May have a protective effect against the risk of diabetes later in life.

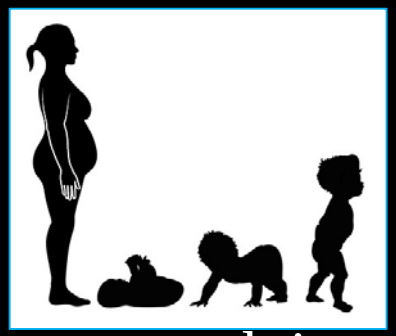
Macrosomia

The incidence of macrosomia is increasing in association with an increased incidence of maternal obesity and diabetes.

Macrosomia is associated with poor perinatal outcomes, particularly asphyxia, perinatal death, birth injury, RDS, and hypoglycemia.

Mitanchez et sl . Best Practice & Research Clinical Obstetrics and Gynaecology (2015)

Research agenda Exposure in utero to maternal diabetes:



More research is needed to better understand the factors that influence fetal growth in case of maternal diabetes and/or obesity.

Studies are needed to differentiate the impact of maternal overweight/obesity from that of maternal diabetes on short-term and long-term outcomes in the mother and in the offspring.

The mechanisms of the long-term impact of maternal diabetes on embryo, fetal, and neonatal physiology are not well established.

Early biomarkers of maternal diabetes imprinting effects in the offspring need to be identified.

Mitanchez et sl . Best Practice & Research Clinical Obstetrics and Gynaecology (2015)