

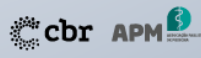
# European Course on Pediatric Neuroradiology in Latin America (ECPNR-LATAM)



3<sup>rd</sup> Cycle - Module 1  
de 1º a 4 de outubro

Local: Sede da APM  
Associação Paulista de Medicina  
São Paulo - Brasil

spr.org.br



## The fetus

*“In-utero acquired pathology”*

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# “Acquired pathology (clastic) vs. genetic”

WHY?



- Counselling for subsequent pregnancies
- Prognosis
- Therapeutic planning (?)

# General patterns of fetal clastic lesions\*

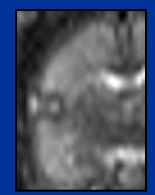
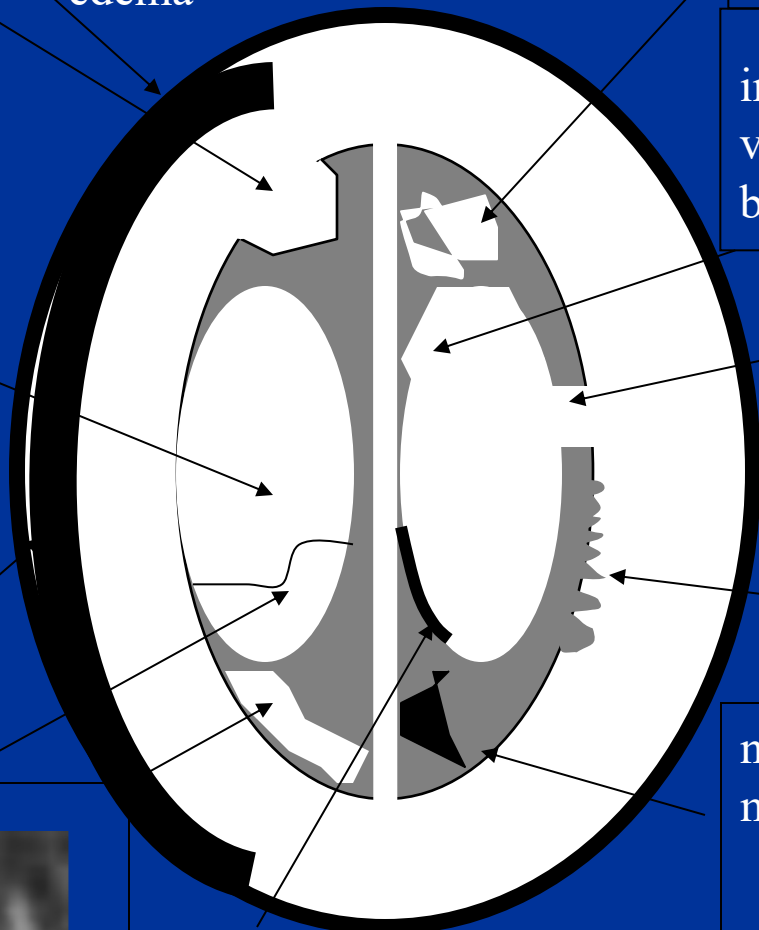
\*CAVEAT:

*genetic based diseases appearing  
as clastic features*

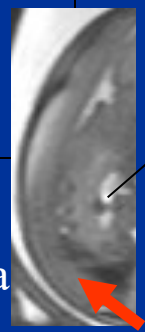
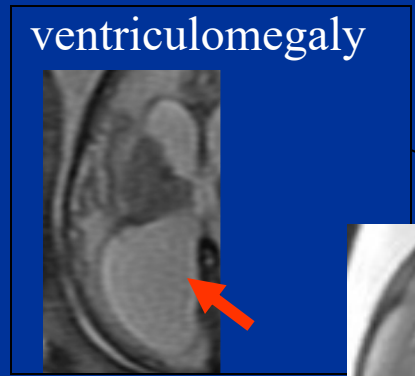
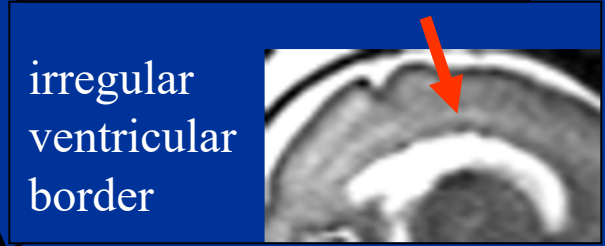
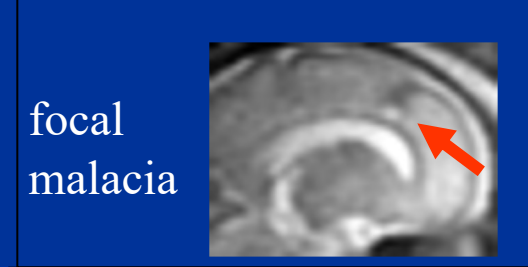
**“Pseudo-TORCH” diseases”**

(genetic+clastic pathophysiology, vascular mediated)

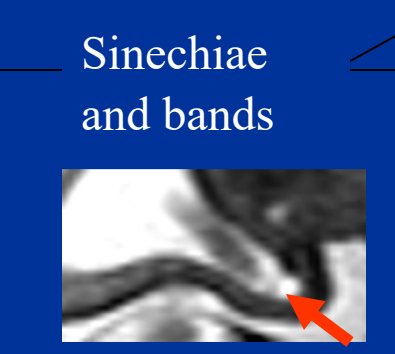
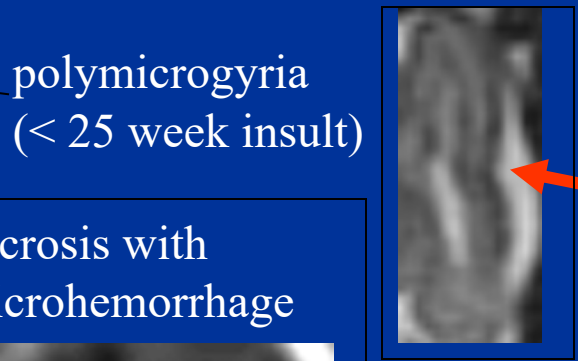
# clastic signs



swelling edema



subdural hematoma



T1

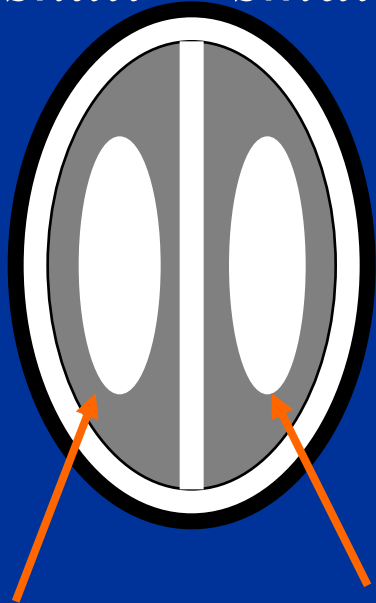


hemosiderine and debris deposits



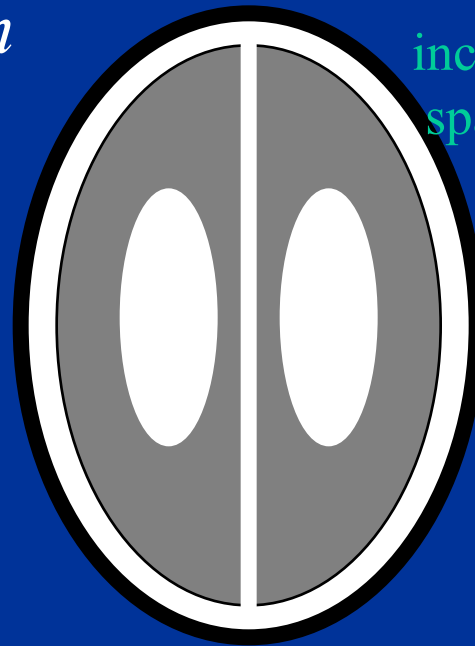
# acquired microcephaly

*microcephaly:*  
*small skull + small brain*



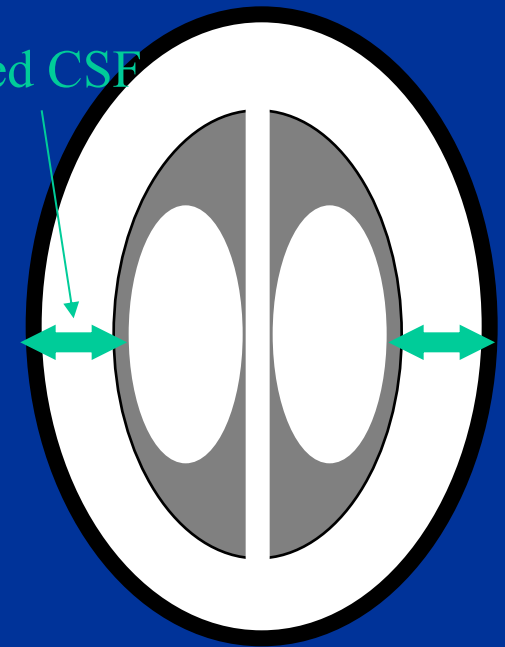
genetic or clastic

normal



*microencephaly*

increased CSF space

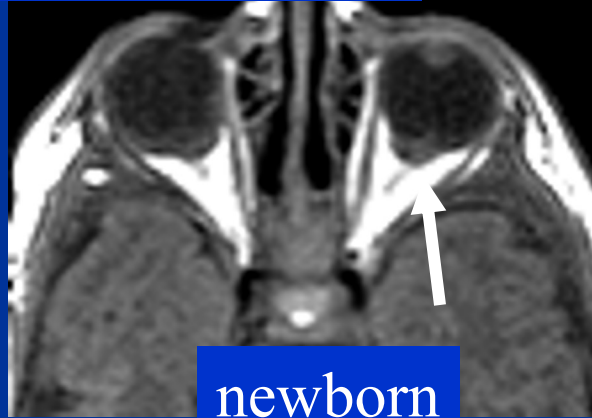
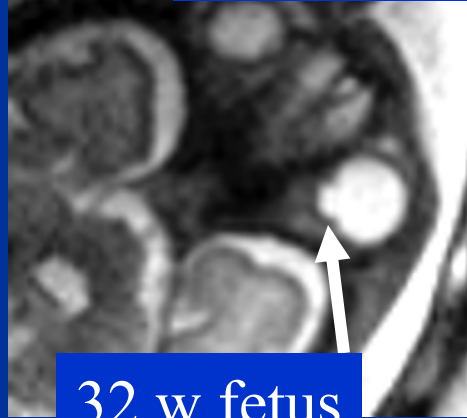


mostly clastic\*

\*pseudo-TORCH

# Associated findings making clastic aetiology unlikely

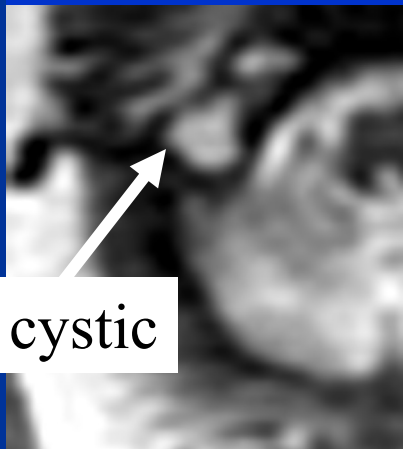
optic nerve head coloboma



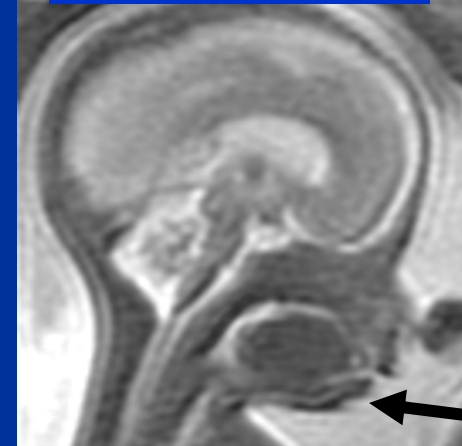
nuchal plique thickening



inner ear malformations



micrognathia



# Aetiology of fetal acquired pathology

- hypoxic, ischemic
- infective, inflammatory
- hemorrhagic, venous congestion, edema
- metabolic

# hypoxic, ischemic

- maternal hemorrhage or acute severe anemia
- placental abruption
- eclampsia, preclampsia, HELLP, maternal shock
- infarction of placenta
- maternal hypoxia, CO intoxication

**maternal side  
causes**

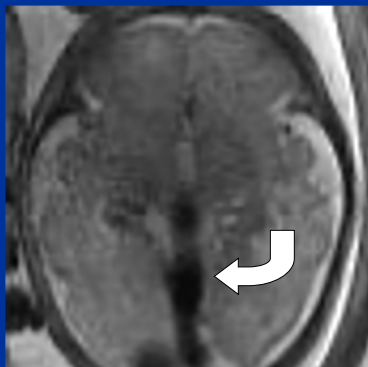
- vascular malformations or fistulae (malf. of Galen)
- vascular steal syndrome
- TTTS, Laser therapy complication, co-twin death
- infections related ischemia
- idiopathic

**fetal side  
causes**

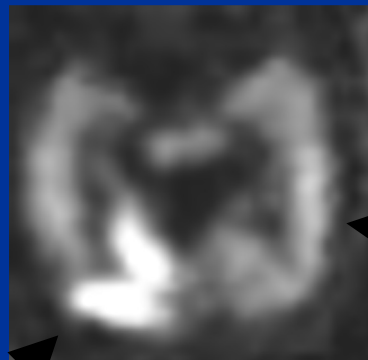
# acute ischemia

Ann Neurol 2002. Baldoli C, Righini A, Parazzini C, Scotti G, Triulzi F.

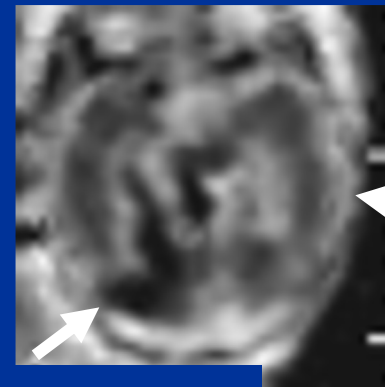
32w female with vein of Galen malformation



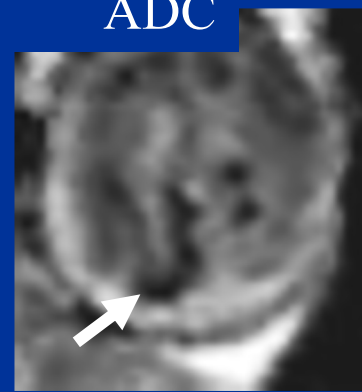
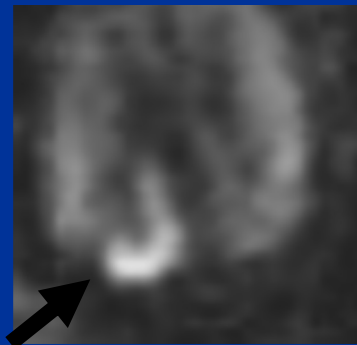
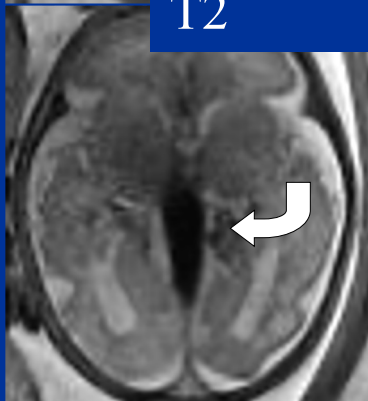
T2



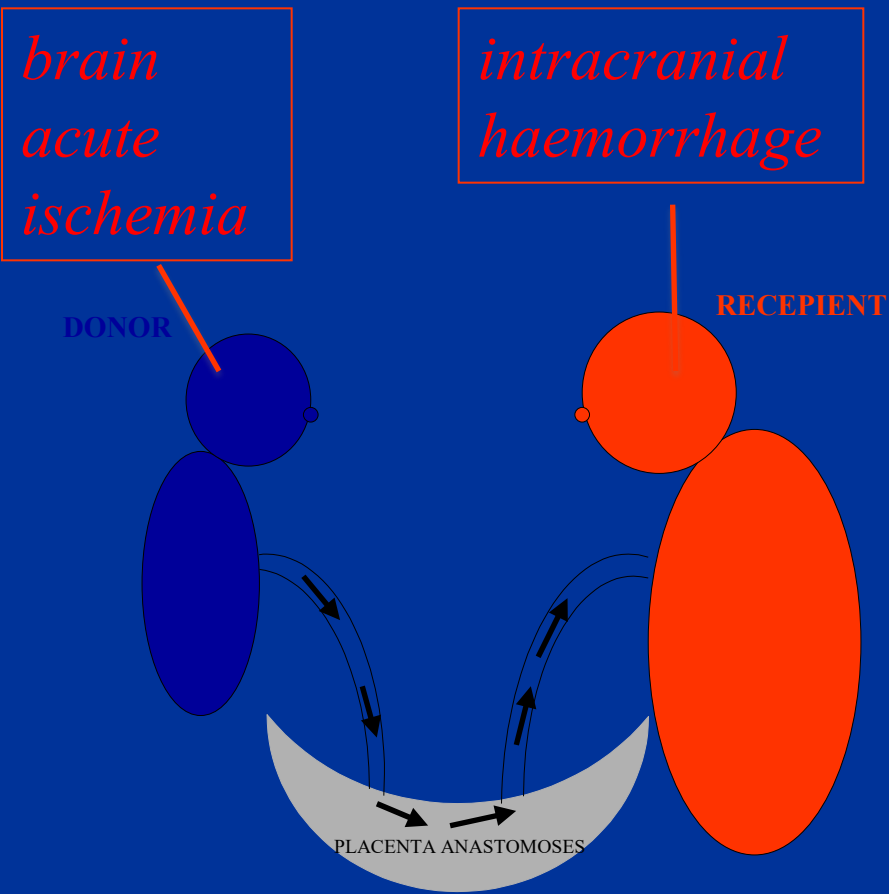
DWI



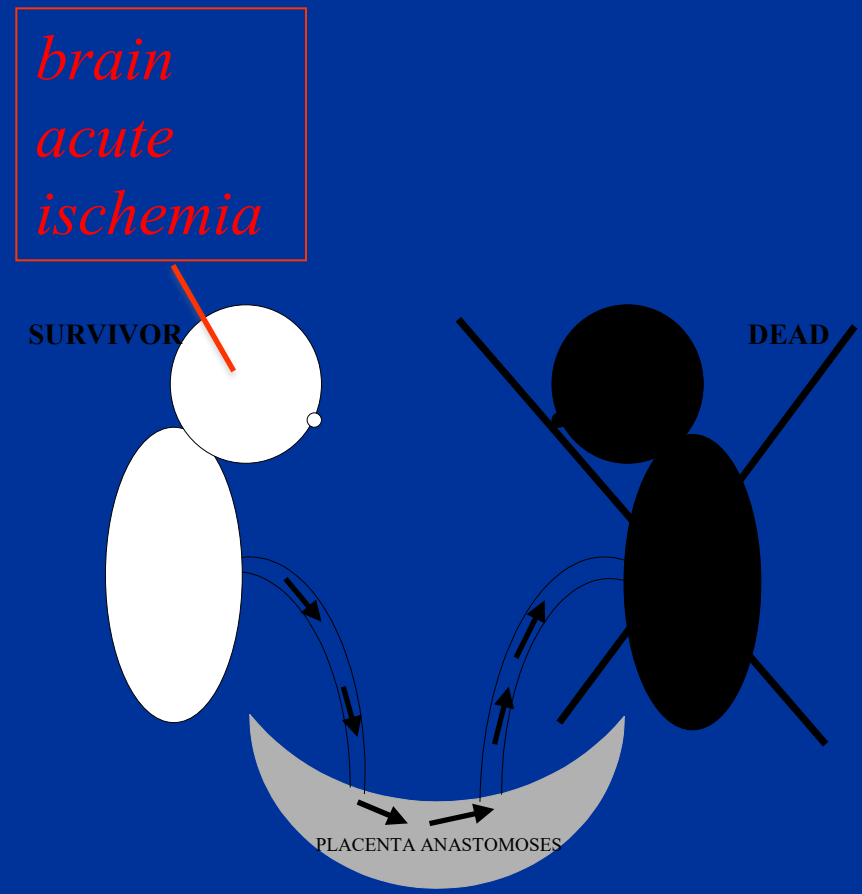
ADC



# *mono chorionic TWINS pathophysiology*



condition 1



condition 2

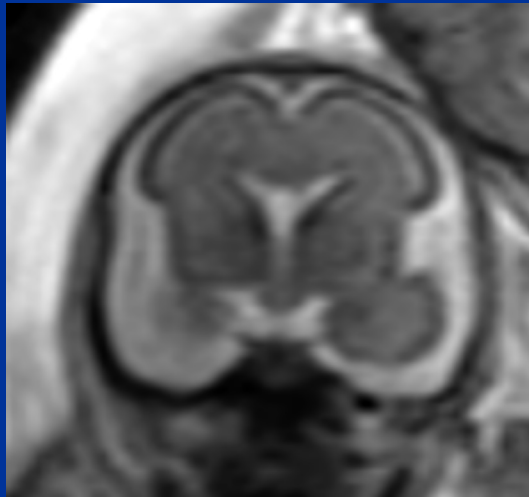


# acute ischemia

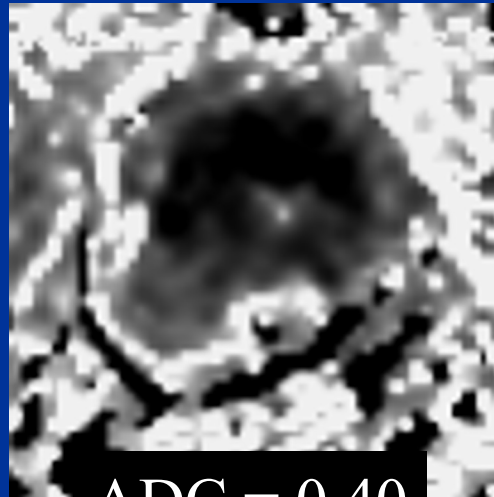
Righini A et al.. Ultrasound Obstet Gynecol. 2007

44 - 4 hours after co-twin death

14 days follow-up

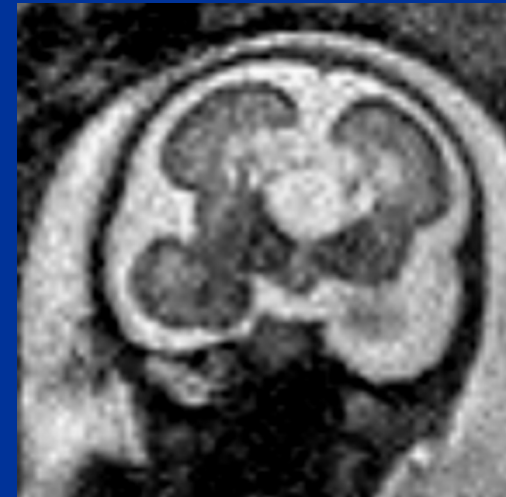


T2w ss-FSE

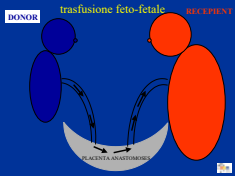


ADC = 0.40

ADC



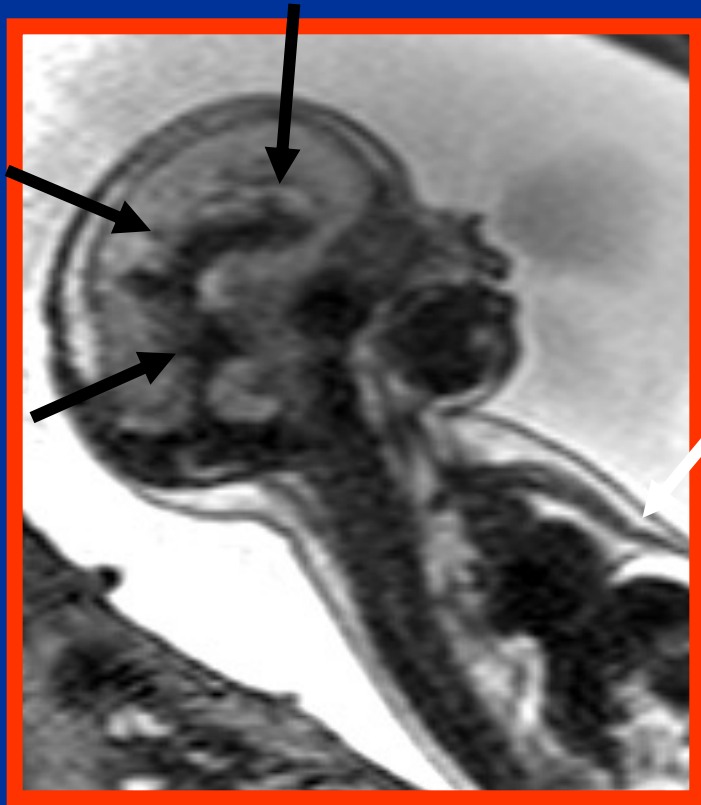
T2w ss-FSE



# acute-subacute ischemia

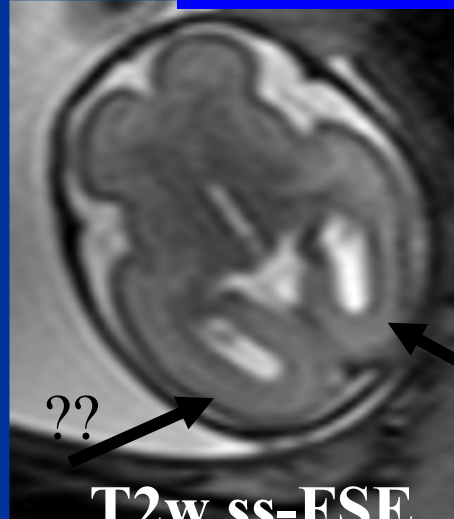
26 week recipient

hydrops, edema, hemorrhage

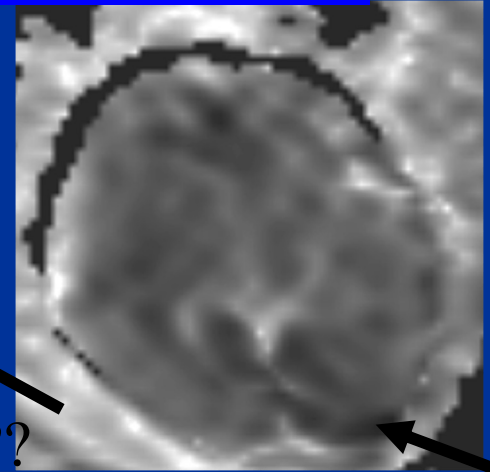


T2w ss-FSE

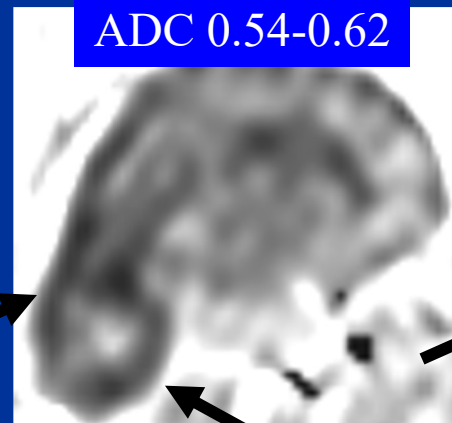
26 week donor TTTS



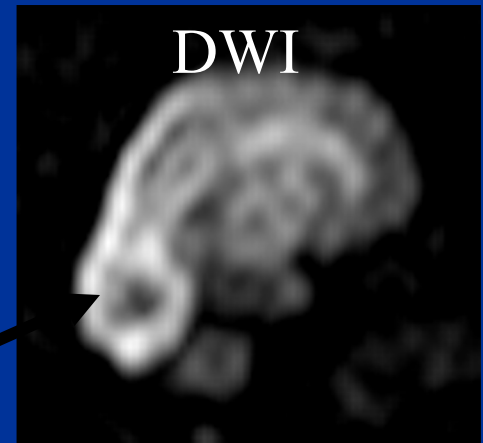
T2w ss-FSE



ADC 0.54-0.62



ADC 0.54-0.62

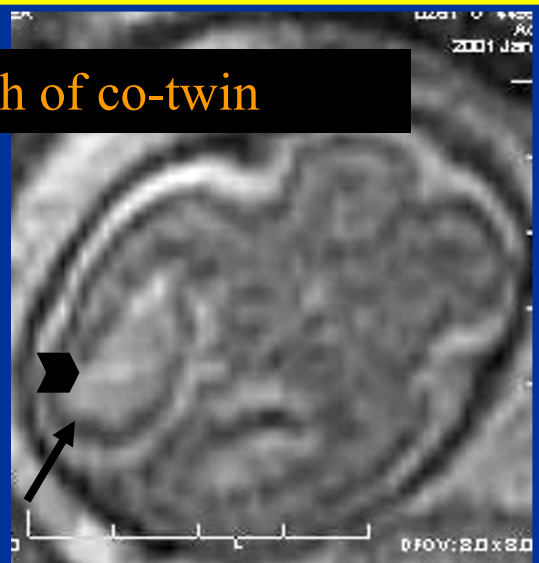
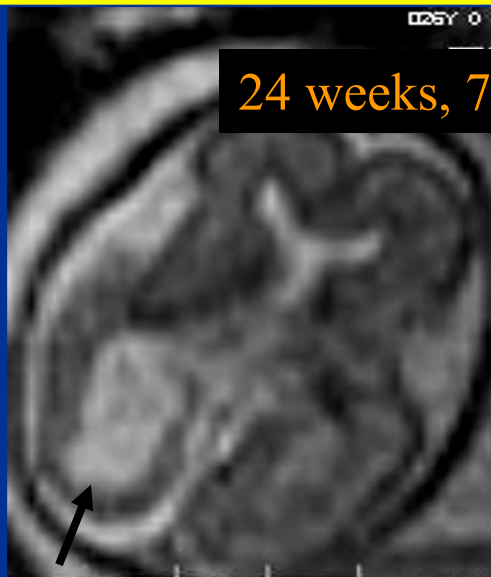


DWI

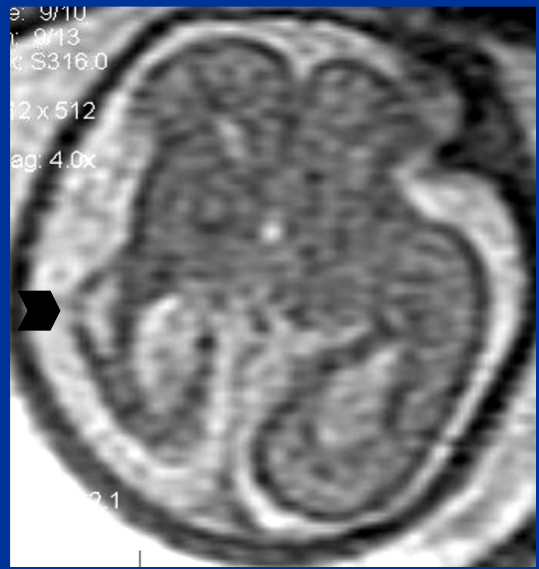


# subacute ischemia

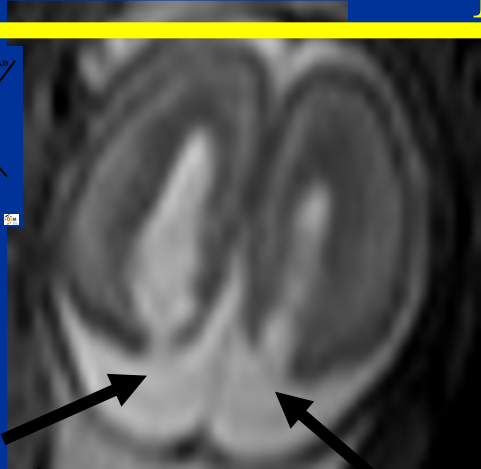
24 weeks, 7 days after death of co-twin



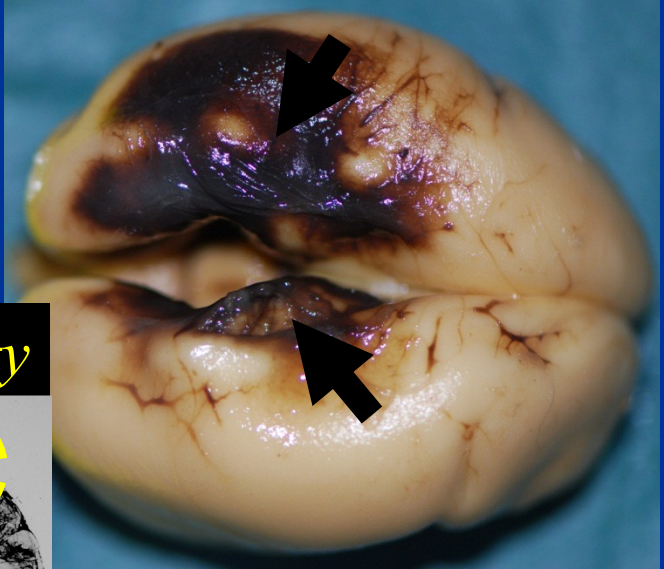
21 days later



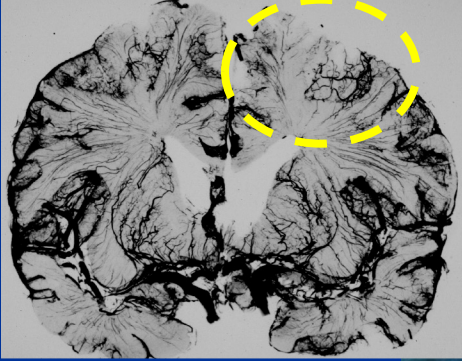
# sequelae of ischemia



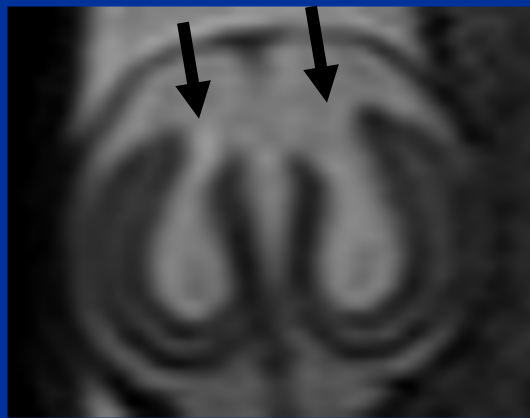
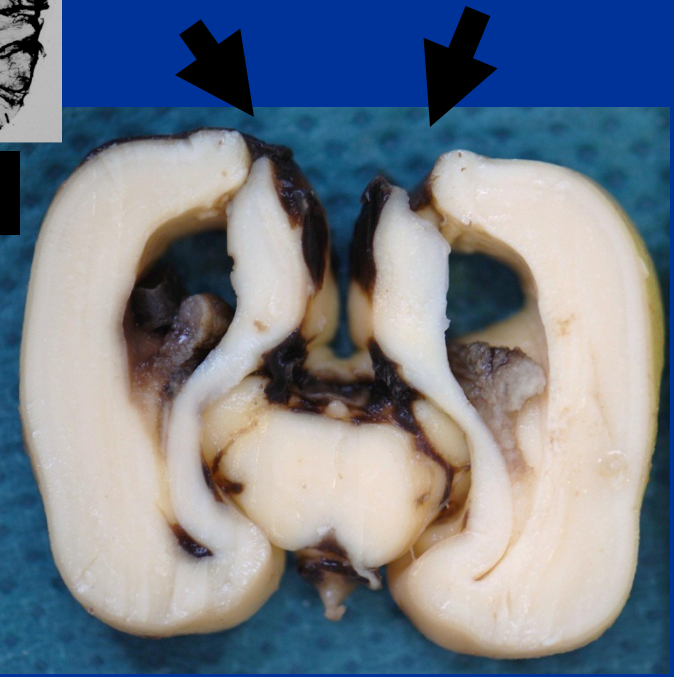
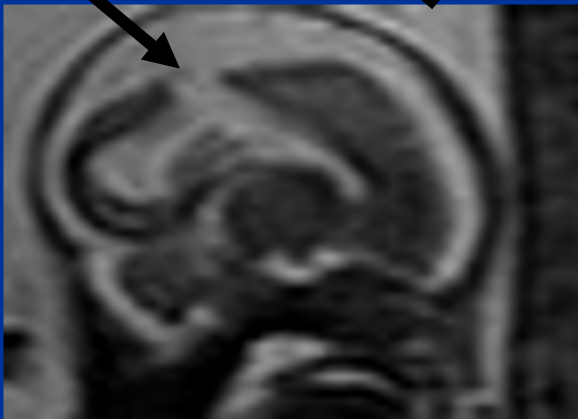
20w survivor, 4w after co-twin death



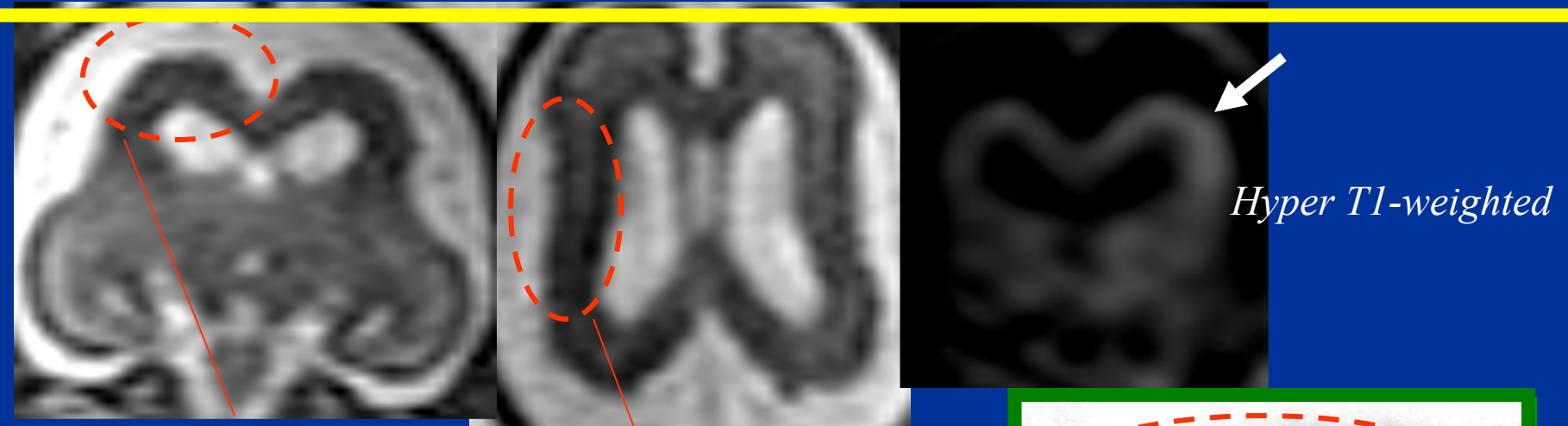
*pathophysiology*



*watershed areas*



# sequelae of ischemia – “plus”

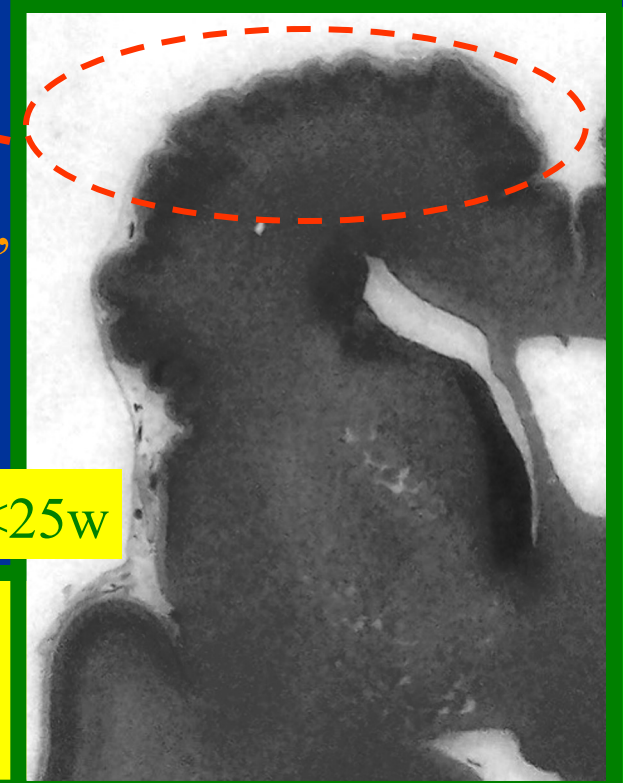


*“saw-tooth like polymicrogyria”*

23 weeks early gestation vaginal bleeding,  
borderline ventriculomegaly

polymicrogyria as “reparative” phenomenon <25w

Pathology:  
ISCHEMIC AETIOLOGY





# sequelae of ischemia – “plus”



21w, monochorionic twin survivor after 5-7 dd death of co-twin and 11 dd after Laser coagulation for IV stage TTTS

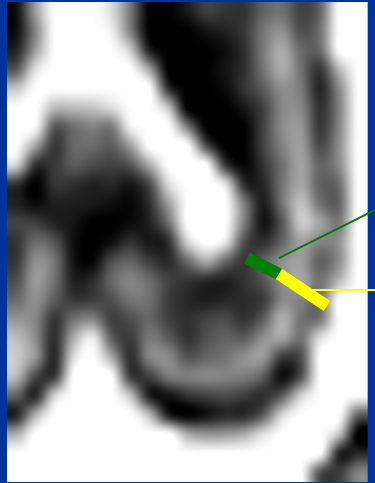
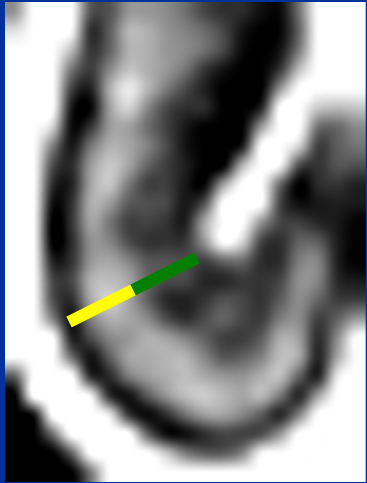
*abnormal infoldings of early phase of polymicrogyria*



21w



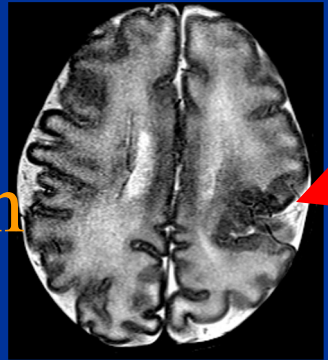
25w

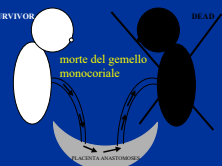


intermediate zone

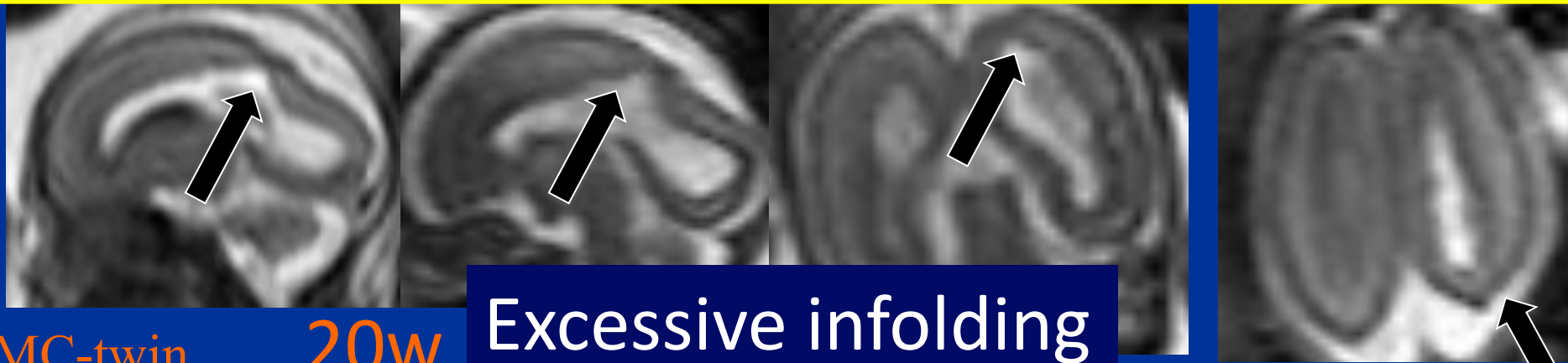
sub-plate

newborn





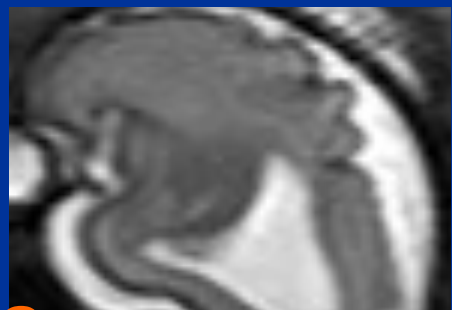
# sequelae of ischemia – “plus”



Excessive infolding

MC-twin  
co-twin  
dead  
between  
16-17 w

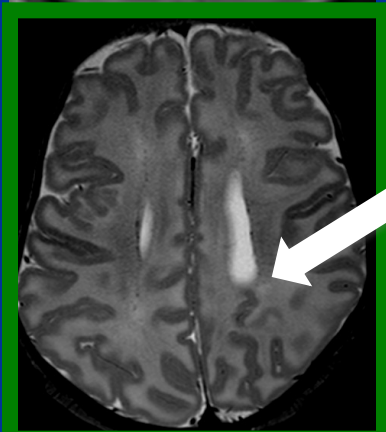
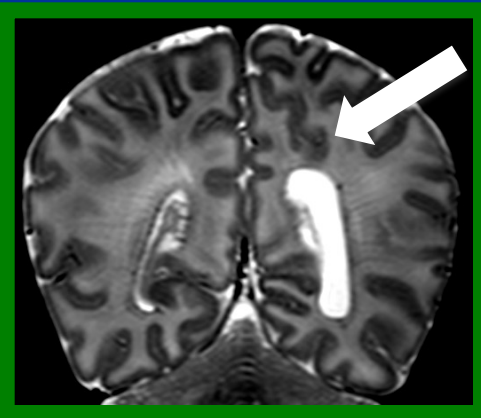
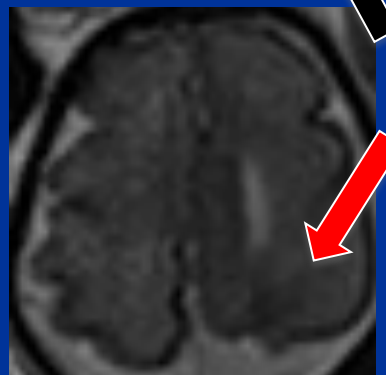
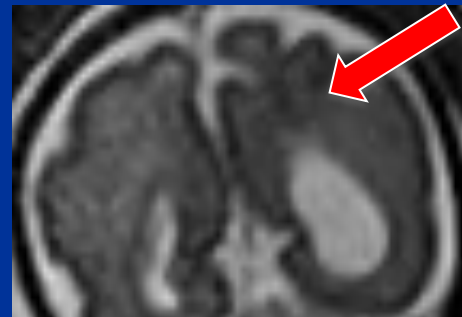
20w



28w

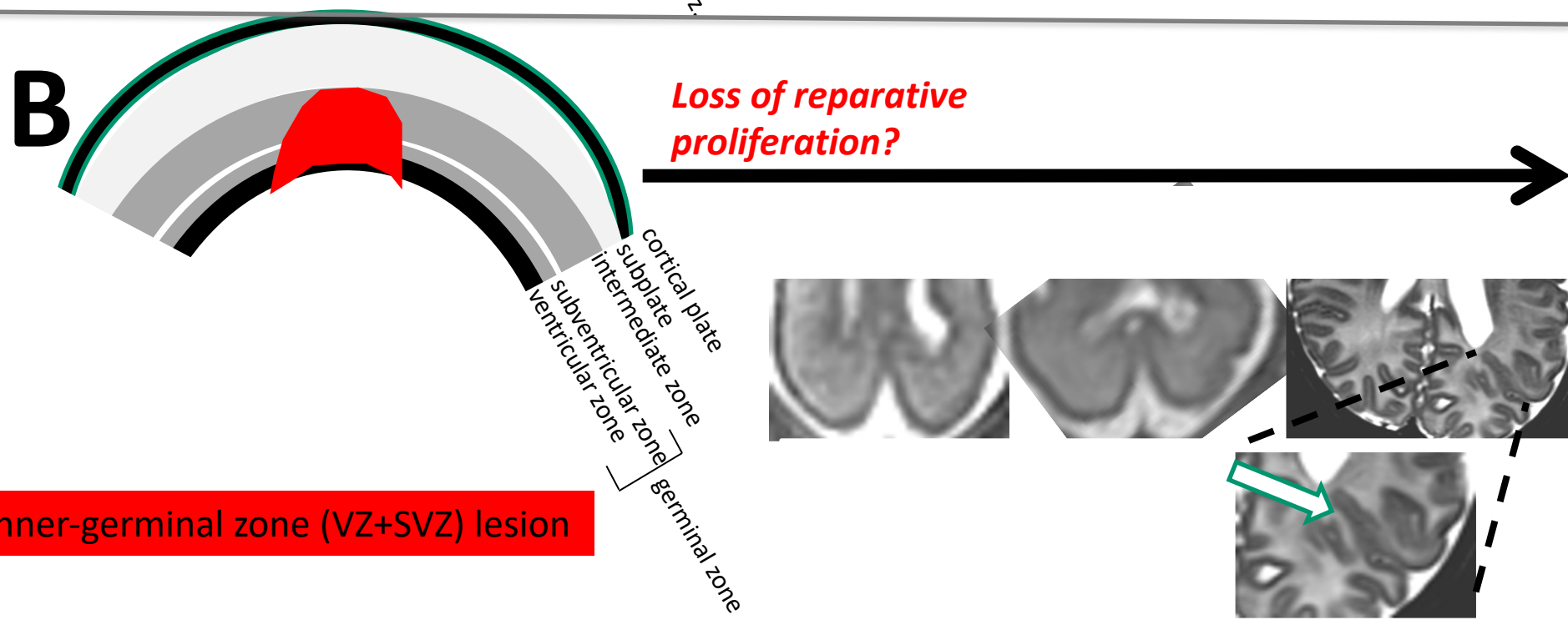
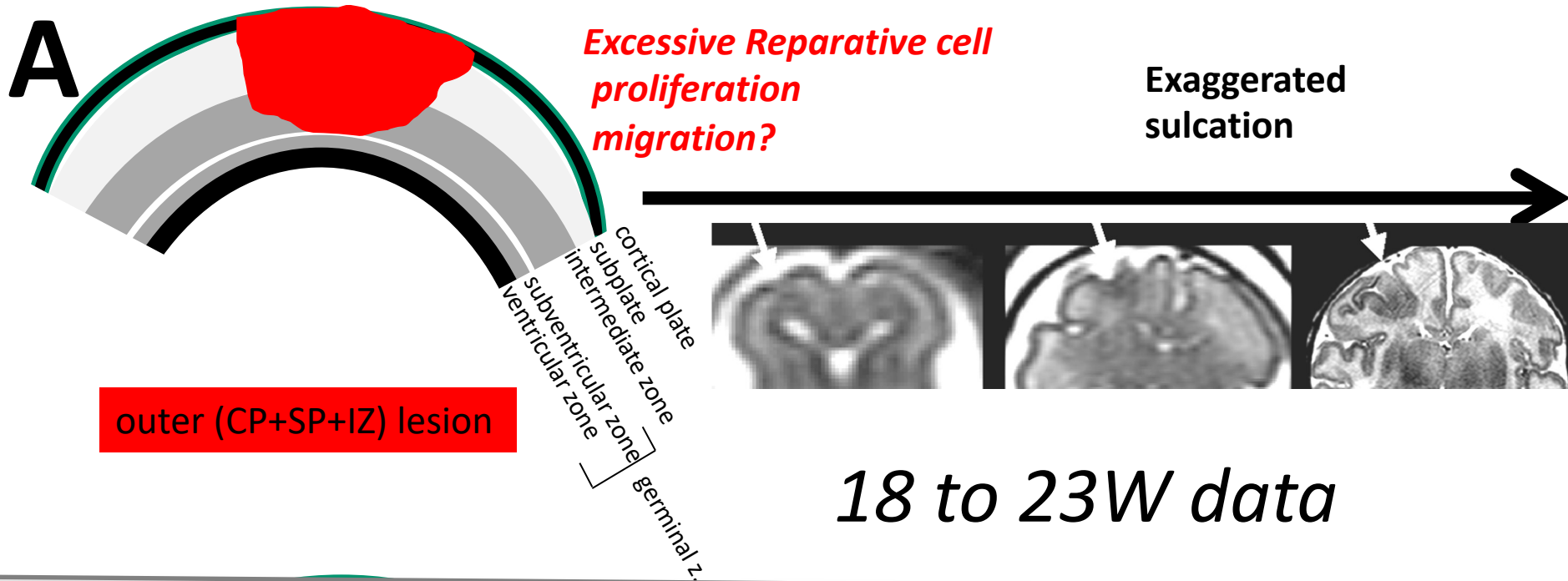


newborn



**Acquired (clastic) focal cortical anomalies.**

*Hypothesis: based on fetal MRI observations*

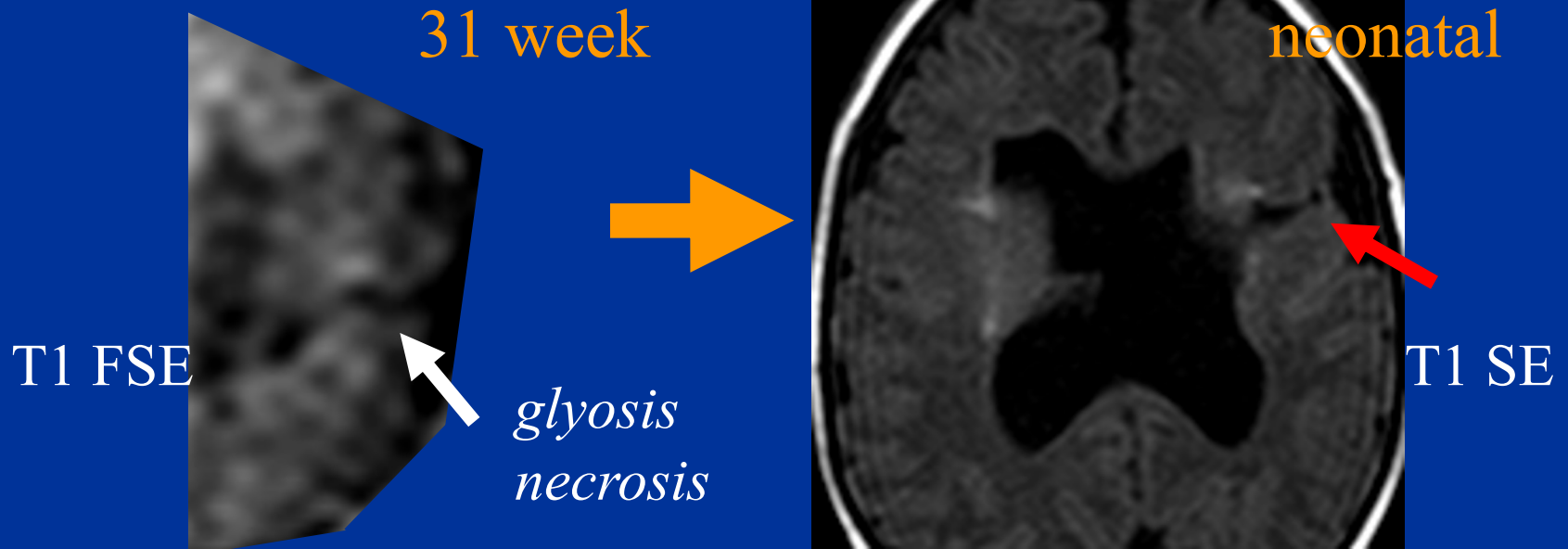


# sequelae of ischemia – “plus”

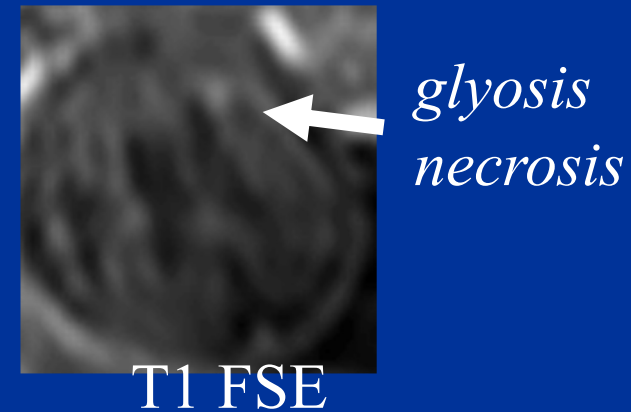
acquired (probable ischemic-haemorrhagic) *schizencephaly*

Evidence of hemorrhage in **83%**.

Nabavizadeh et al AJNR 2014



23w,  
ventriculomegaly,  
plexus hyper at US



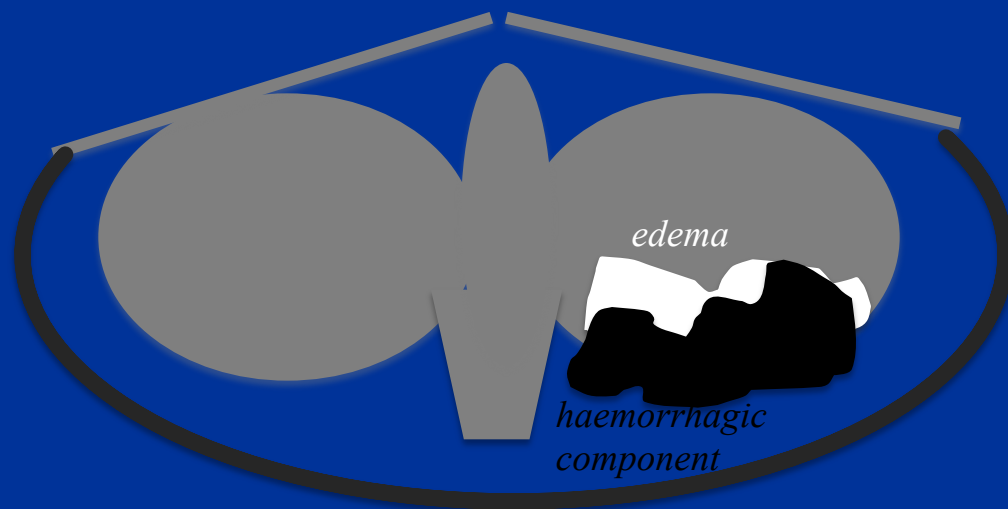
# POSTERIOR FOSSA LESIONS

## Cerebellar ischemic-haemorrhagic lesions 1

Righini et Al  
Eur. Radiol., 2015

17 cases cohort

stage	7 acute/subacute	10 chronic
site	8 unilateral	9 bilateral
position	13 caudal	4 caudal +cranial
depth	13 superficial	4 superficial +deep
vermis involvement	10 involved	7 not involved
pontine atrophy	2 present	15 absent
vascular anomalies	3 present	14 absent
other lesions	4 present	13 absent



- Occurrence in early fetal life before 26<sup>th</sup> week
- Mostly unknown etiology, possible association with generalized body edema and intra-extracranial venous engorgement, caused by viral infection, anemia and heart overload

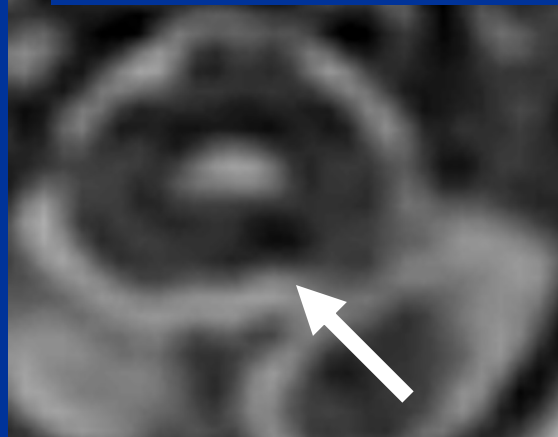
# cerebellar ischemic-haemorrhagic lesions 2

*(one of main cause of hemocerebellar hypoplasia* *Poretti A. et Al., Neuropediatrics. 2008* *)*

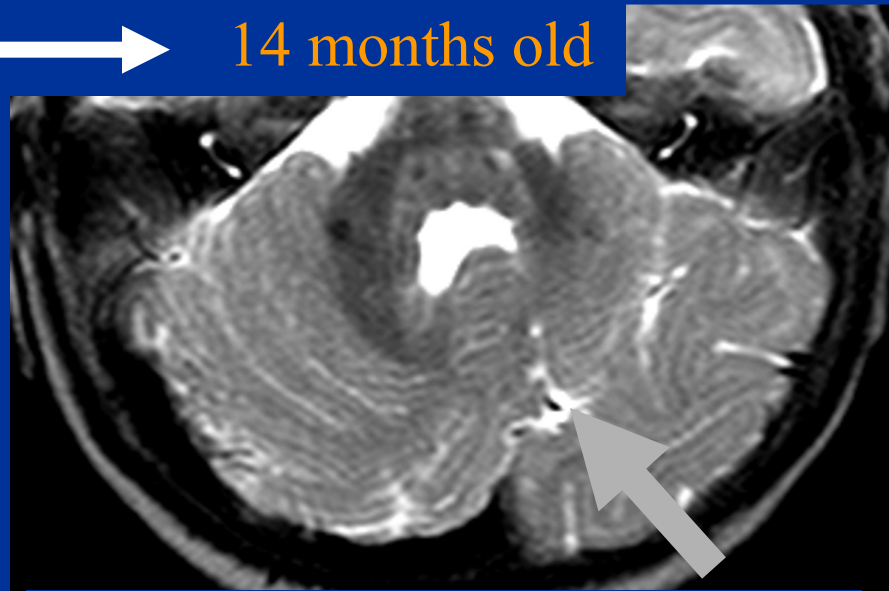
22 w



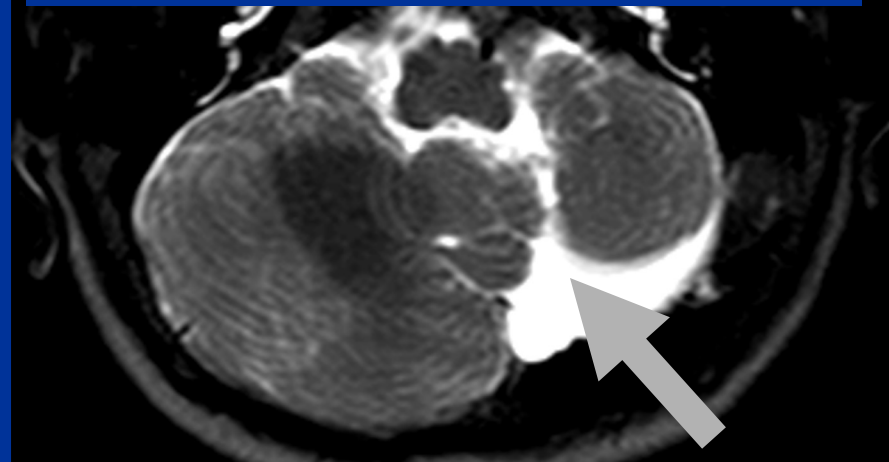
14 months old



*necrosis and parenchymal loss*

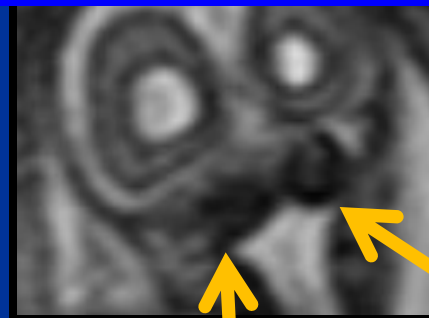
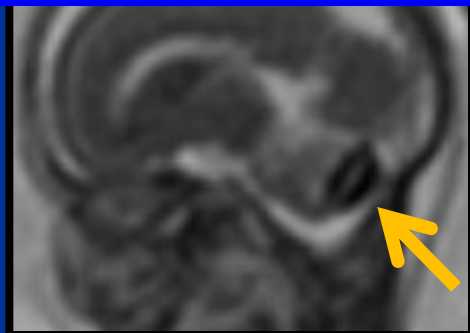


*malformative sequelae*



# cerebellar ischemic-haemorrhagic lesions 3

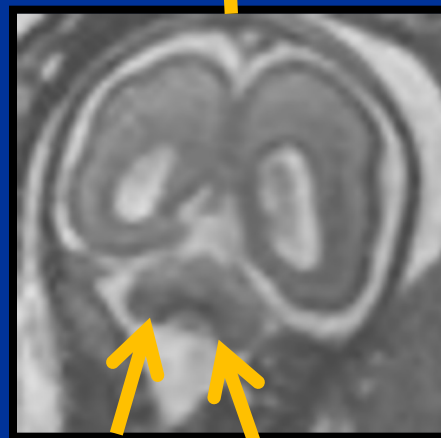
21w GA



acute/subacute



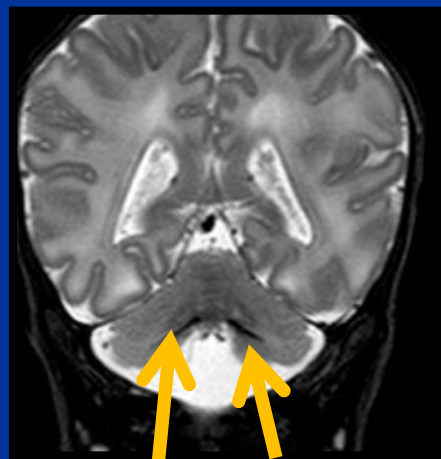
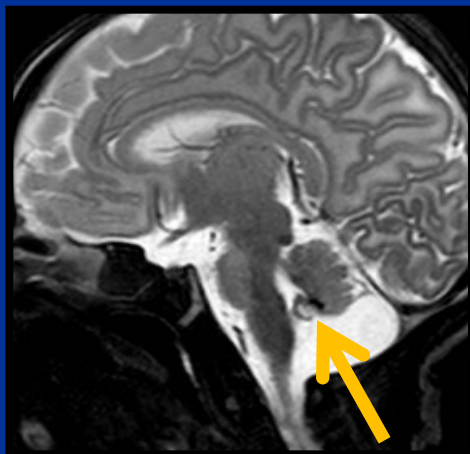
25w GA



chronic



neonate

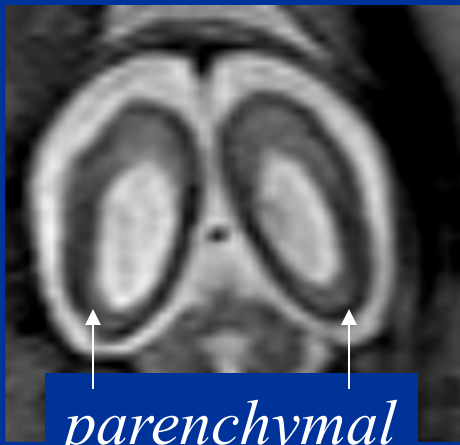


outcome

# infective, inflammatory

- Cytomegalovirus
- Toxoplasmosis
- Parvovirus, Rubella
- Unknown
- *ZIKA*

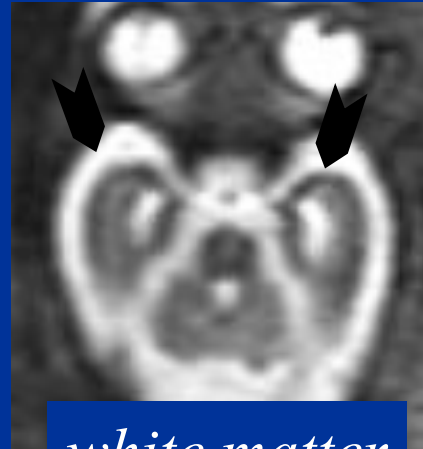
# *Cytomegalovirus: I and II trimester infection*



*parenchymal  
loss*

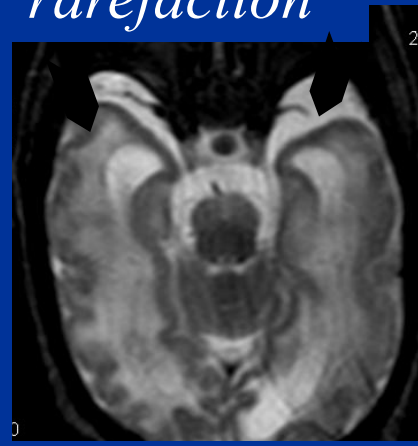
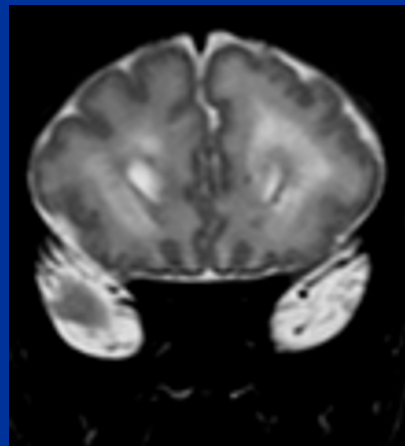
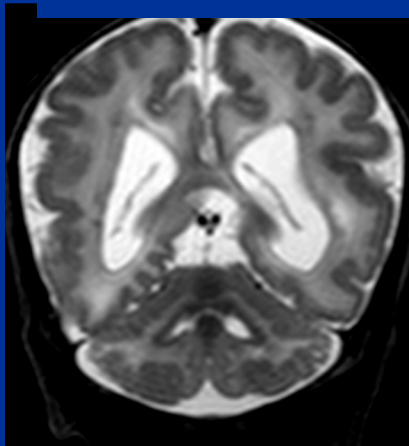


*“plus”  
polymicrogyria*



*white matter  
rarefaction*

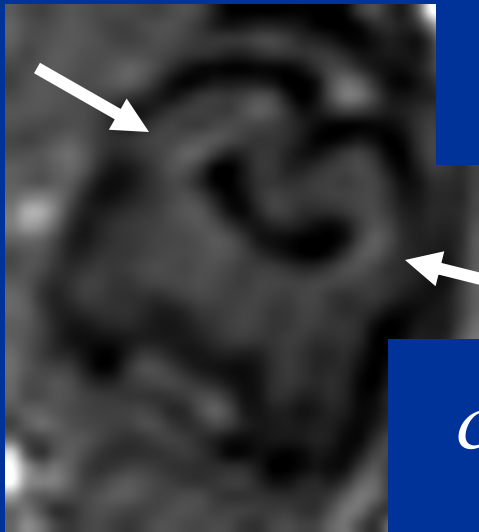
*25w*



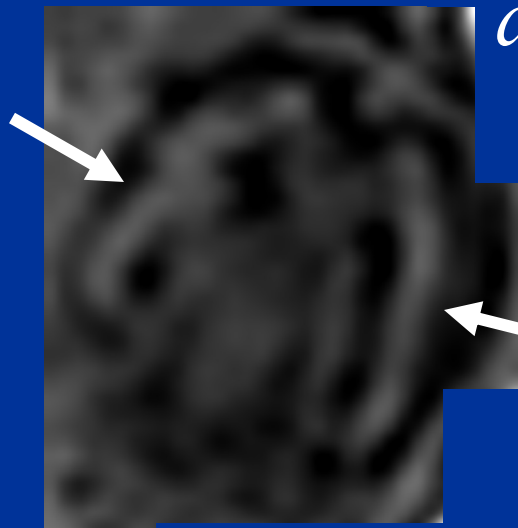
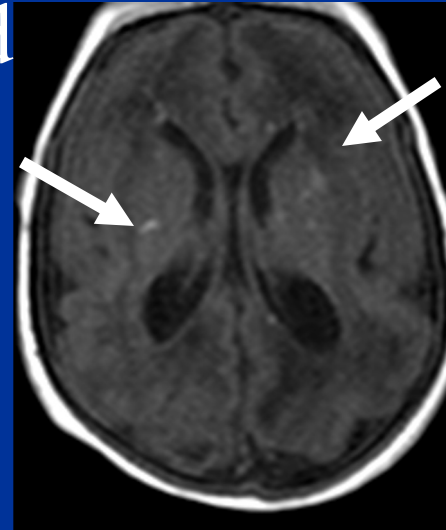
*newborn*

# *Cytomegalovirus: I and II trimester infection*

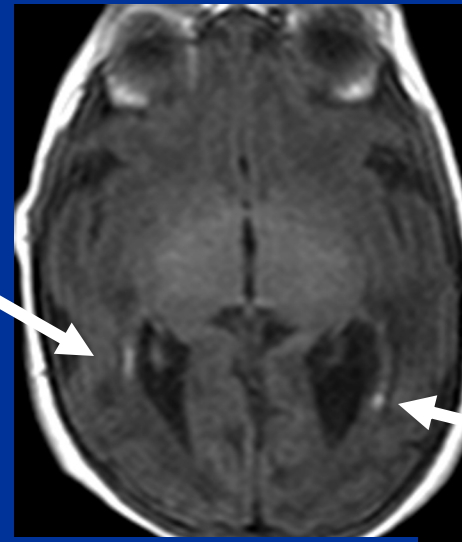
T1-weighted



*calcifications  
and necrosis*



**25w**



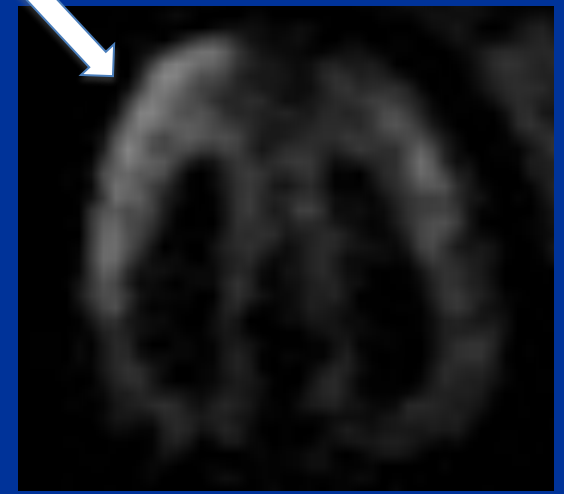
**newborn**

# CMV acute-subacute cerebritis

21w



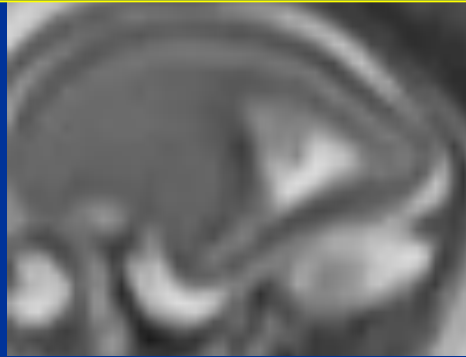
*ongoing tissular injury*



**Diffusion MR**

# CMV "minor" lesions time course

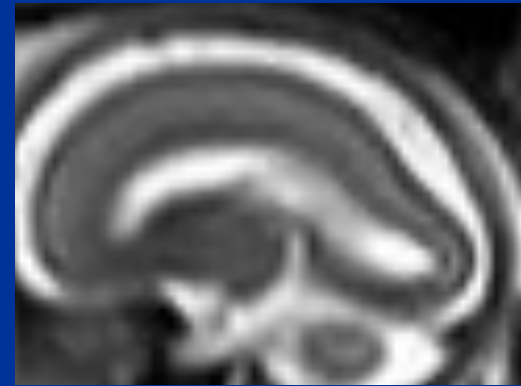
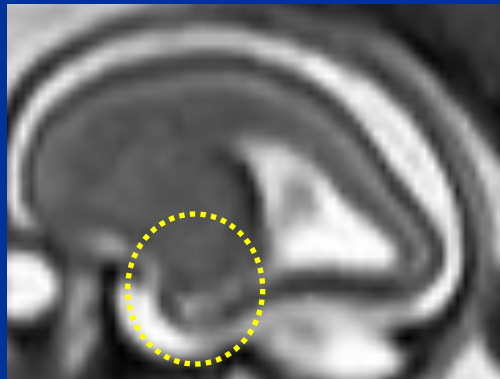
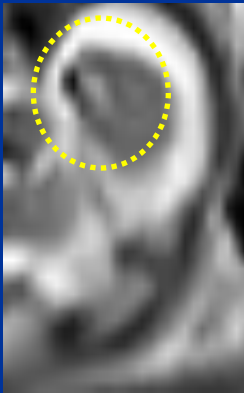
20w



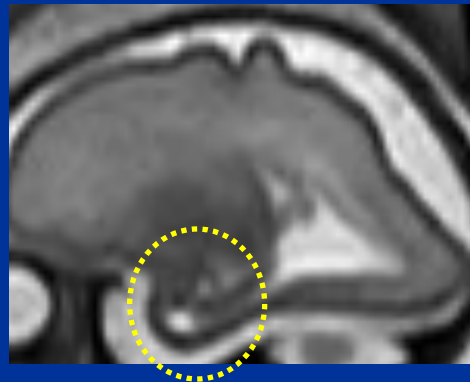
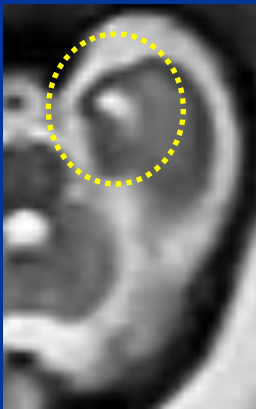
no  
lesions



22w



29w



# *CMV: late infection and “minor” lesions*

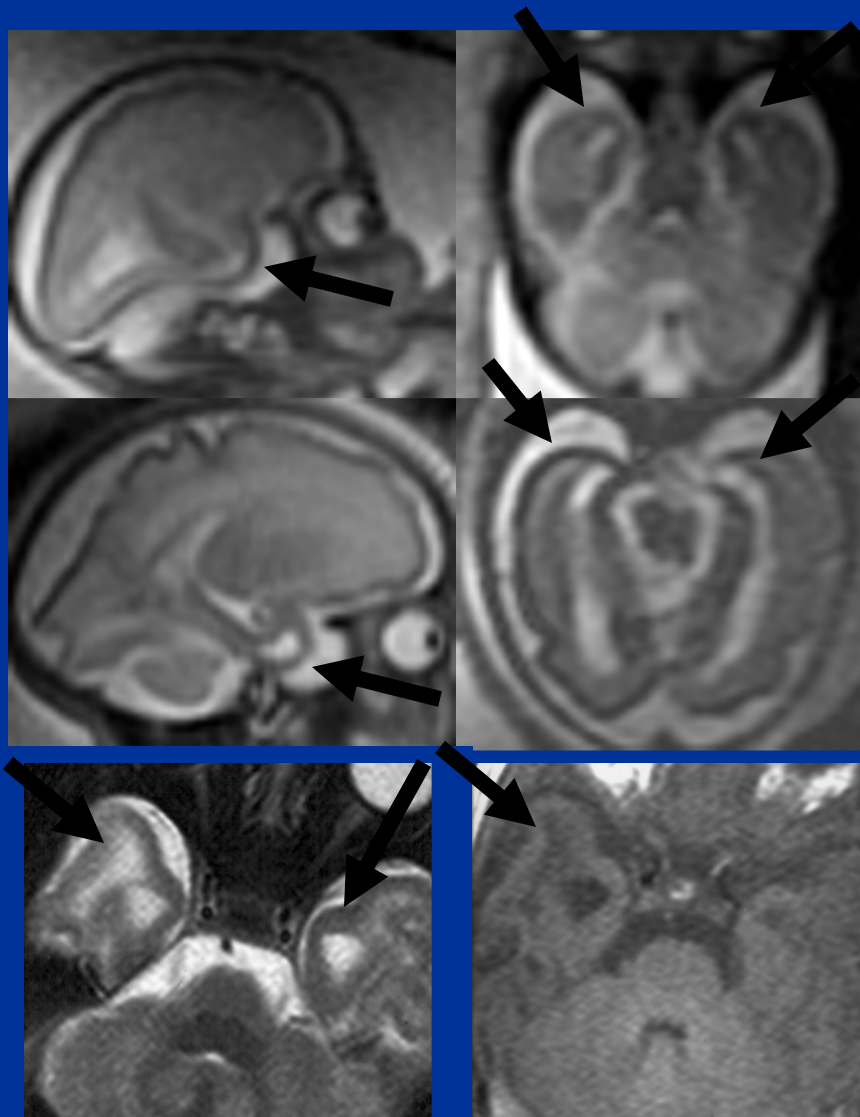
26w



30w



newborn



*Isolated temporal white matter rarefaction and temporal horns enlargement.*

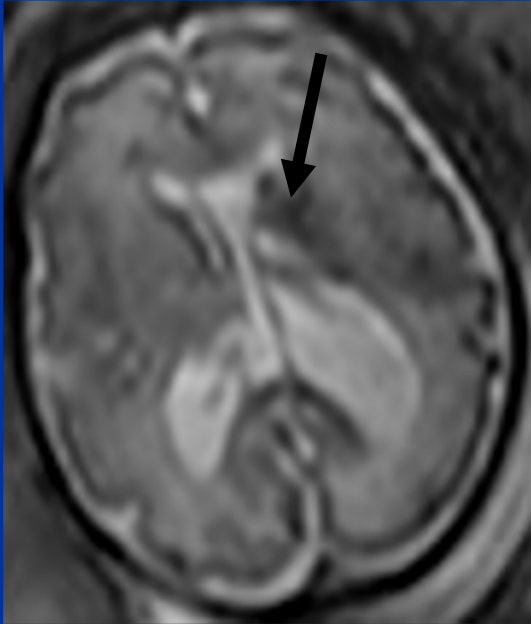
**“Prognosis?”**

# *CMV “minor” lesions: PROGNOSIS*

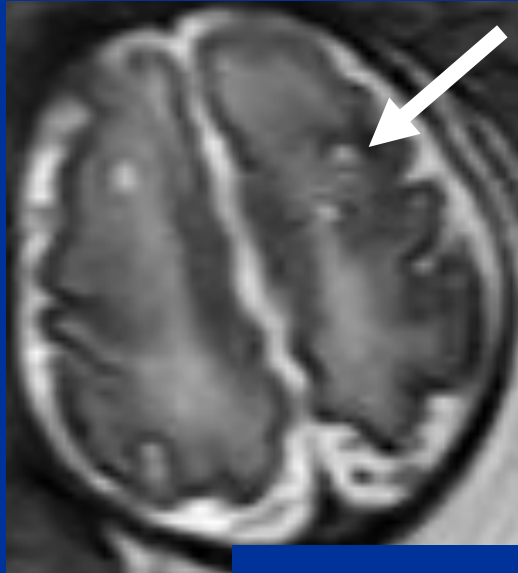
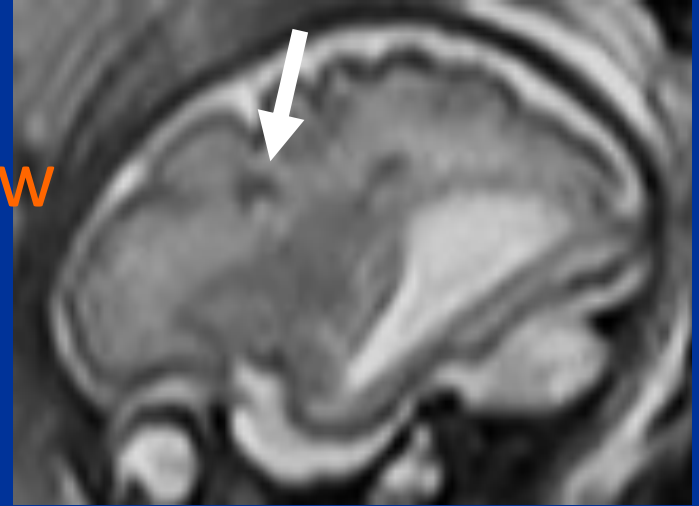
- 40 fetal cases.
- Frequency of minor lesions increased with GA.
- At 5 yrs follow-up **unilateral hearing loss (35%)** or **minor cognitive-behavioural disorders (42%)**.



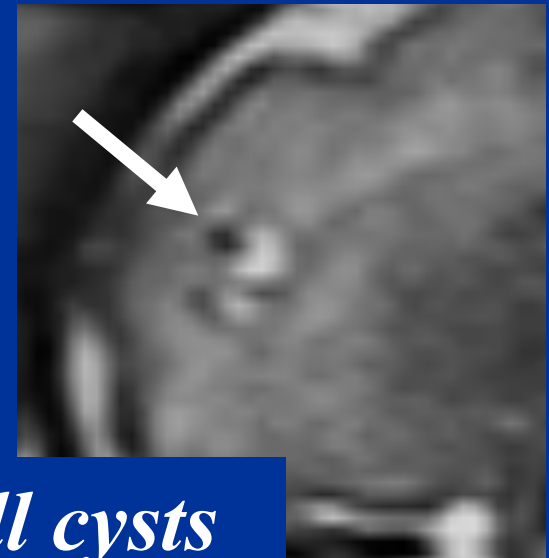
# *toxoplasmosis*



TOXO infection  
between 22-27w



31w, F



*foci of necrosis and small cysts*

# ZIKA virus and severe microcephaly

- ZIKA: flavivirus (family of yellow fever, west Nilus, Dengue)
- Transmission: transplacental, bite of moschitos, Sex (6 months in sperm after infection), transfusion
- 80% cases are asymptomatic
- Microcephaly first-second trimester in up 13% cases

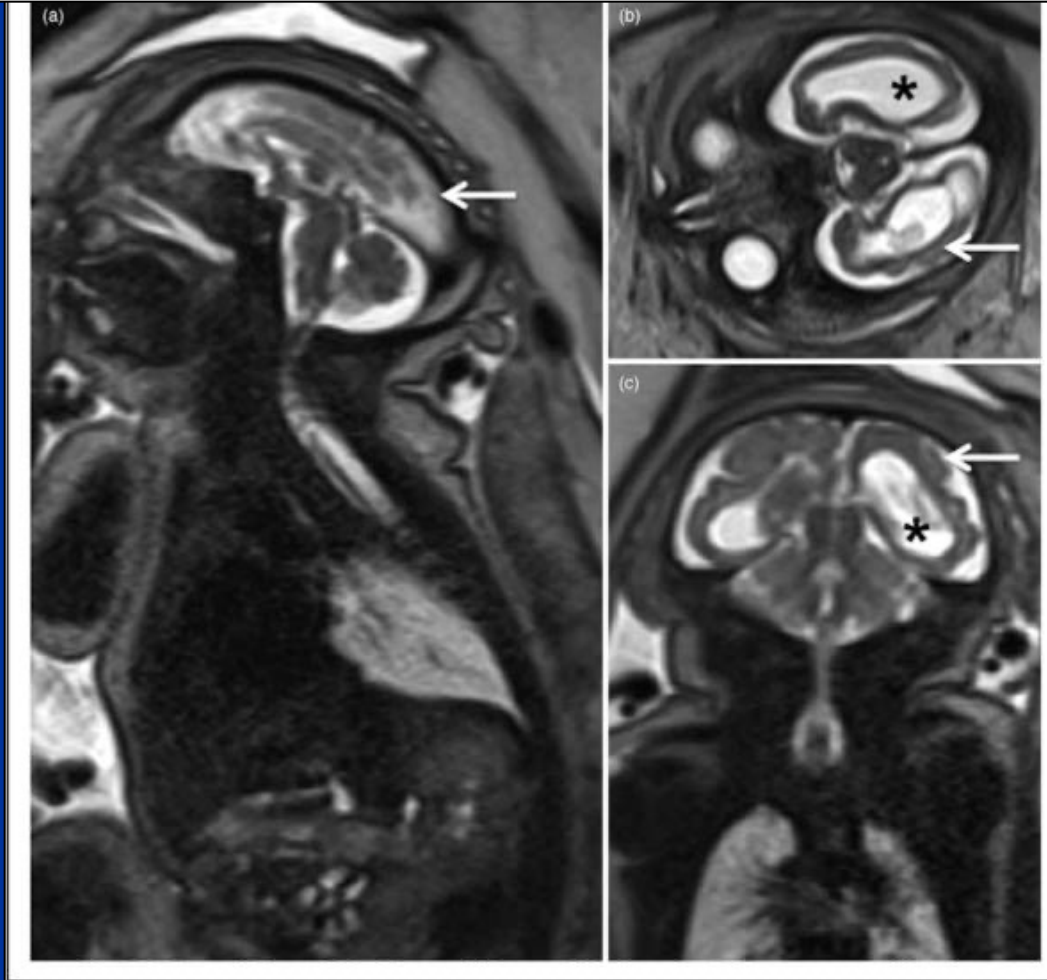
## Congenital Zika syndrome

- **severe microcephaly**
- anomalies of CNS (calcifications, PMG)
- visual impairment
- arthrogriposis

# Prenatal imaging findings in fetal Zika virus infection.

Araujo Junior, Edward; Carvalho, Francisco; Tonni, Gabriele; Werner, Heron

Current Opinion in Obstetrics & Gynecology 2017.



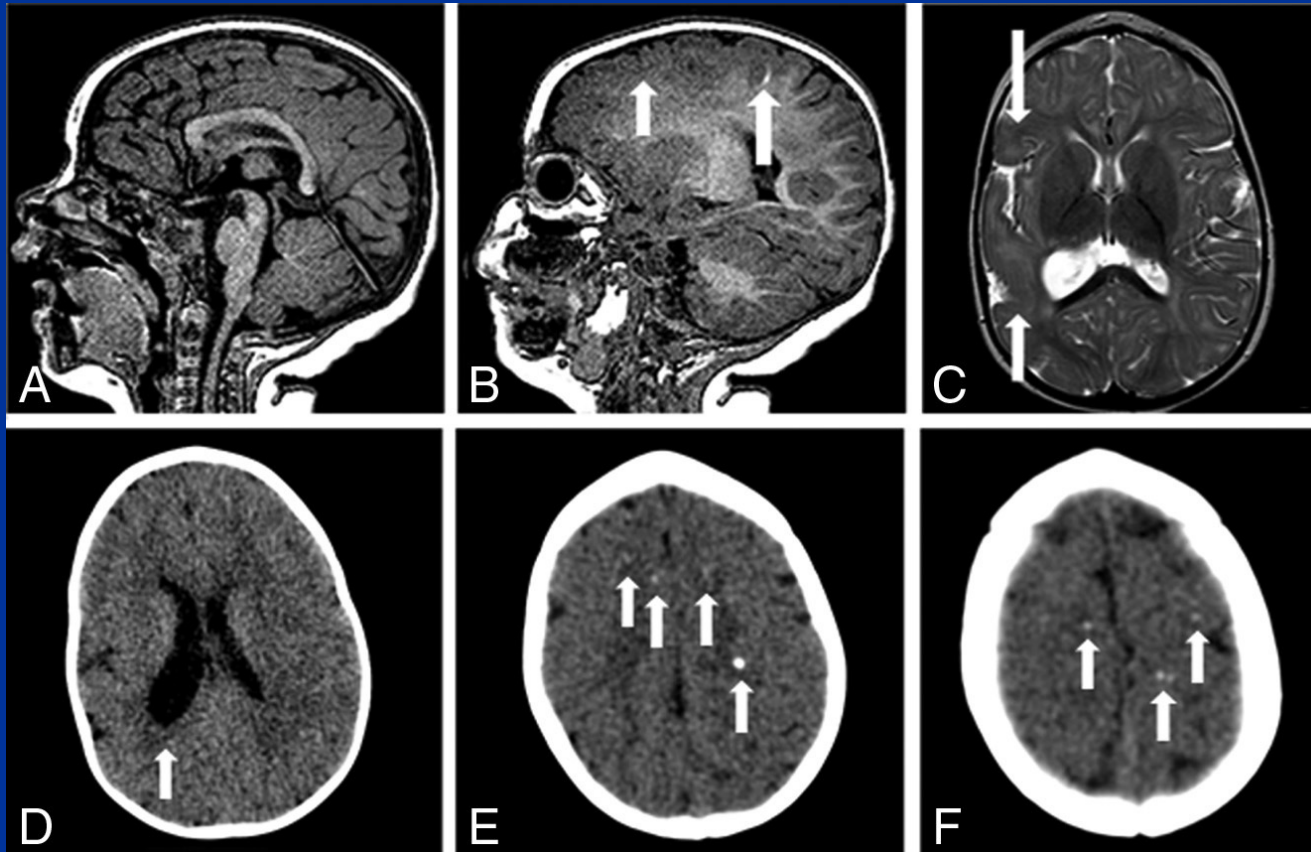
37 weeks: microcephaly, ventricular dilatation  
smoothness of the brain surface and cortical atrophy

# ZIKA cases WITHOUT MICROCEPHALY

Nonmicrocephalic Infants with Congenital Zika Syndrome Suspected Only after Neuroimaging Evaluation Compared with Those with Microcephaly at Birth and Postnatally: How Large Is the Zika Virus “Iceberg”?

X M.F.V.V. Aragao et Al..

AJNR Am J Neuroradiol 2017



Infants with normocephaly presented with asymmetric frontal polymicrogyria, calcifications in the cortico-subcortical junction, mild ventriculomegaly, and delayed myelination.

In postnatal microcephaly, the only abnormalities not seen were a simplified gyral pattern and calcifications outside the cortico-subcortical junction.

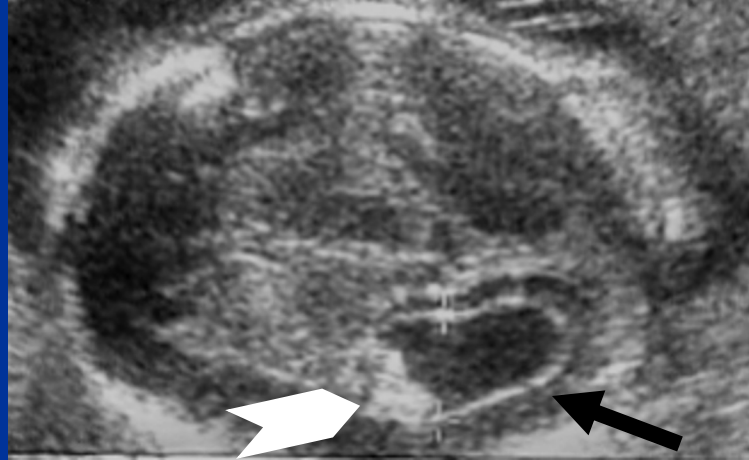
# **A - haemorrhages**

- **idiopathic**
- **coagulation factor deficit (II, V of Leyden etc.)**
- **thrombocytopenia alloimmune**

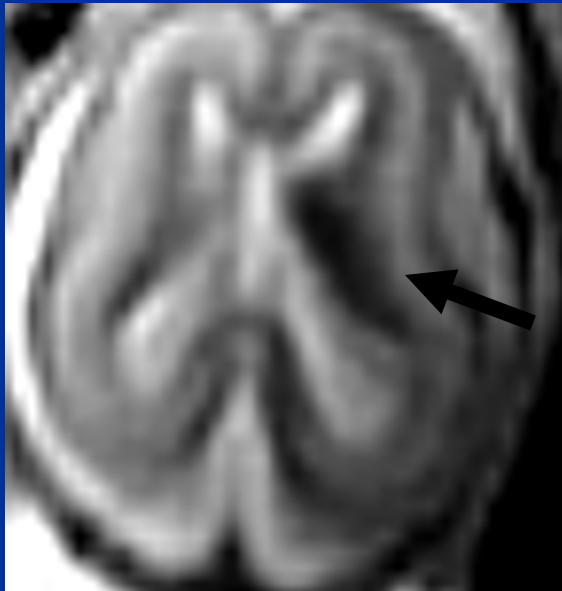
**B - venous congestion,  
edema**

# IVH - parenchymal involvement

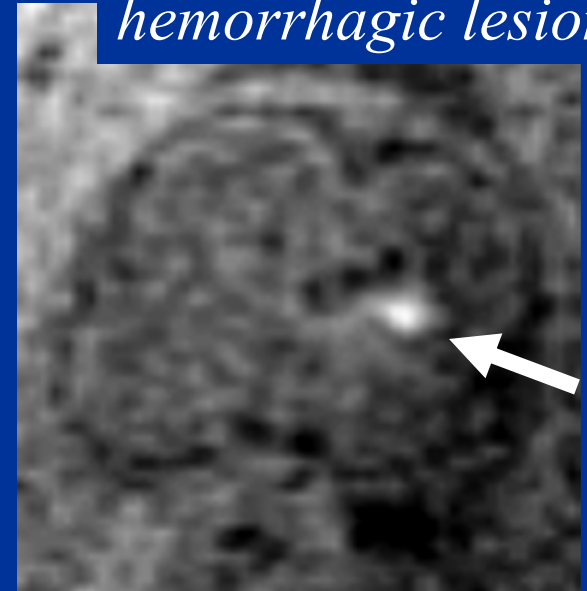
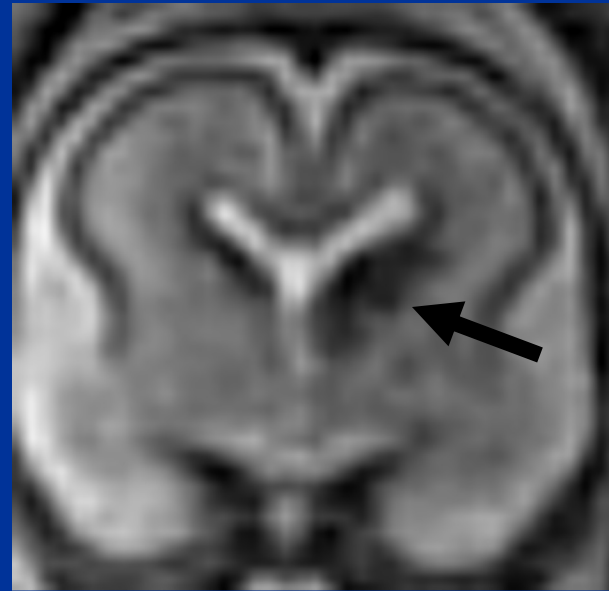
21w, bilateral borderline ventriculomegaly, focal hyperechogenic ventricular margin



*parenchymal  
hemorrhagic lesion*



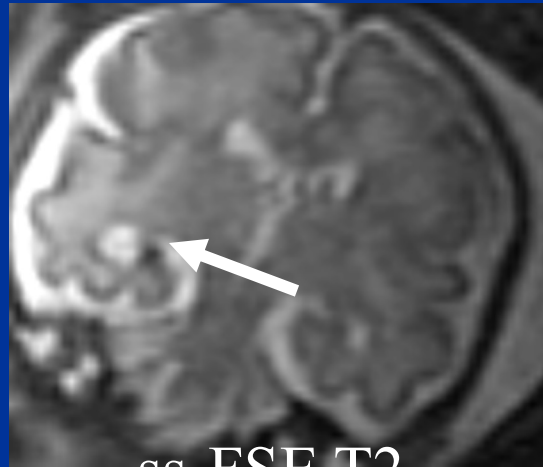
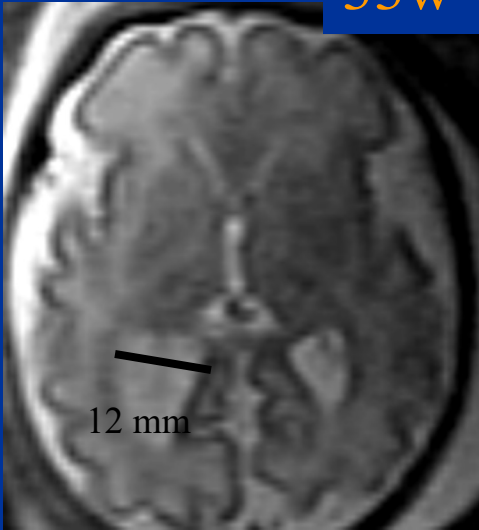
ss-FSE T2



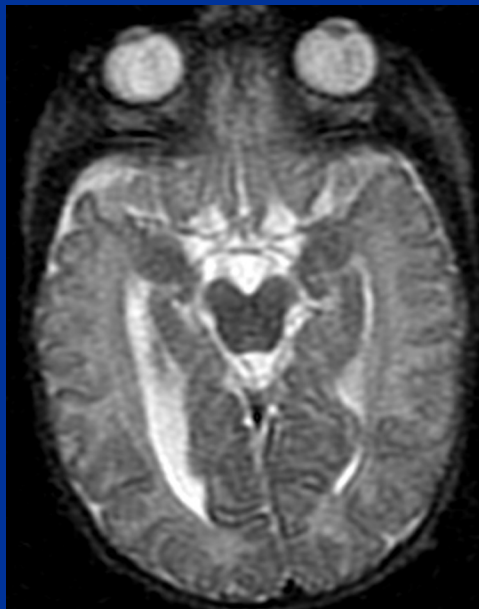
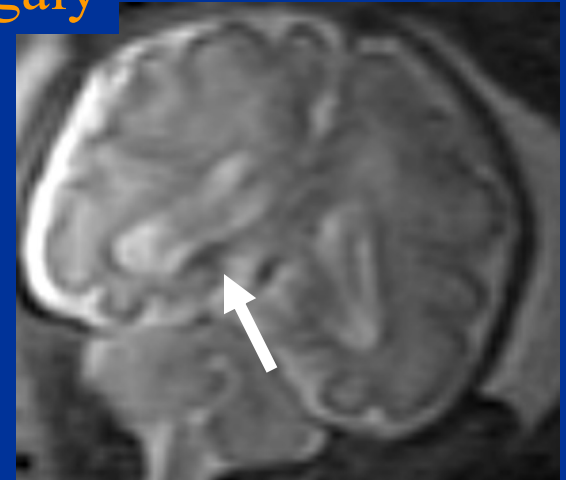
FSE-T1

# IVH grade I and mild borderline ventriculomegaly

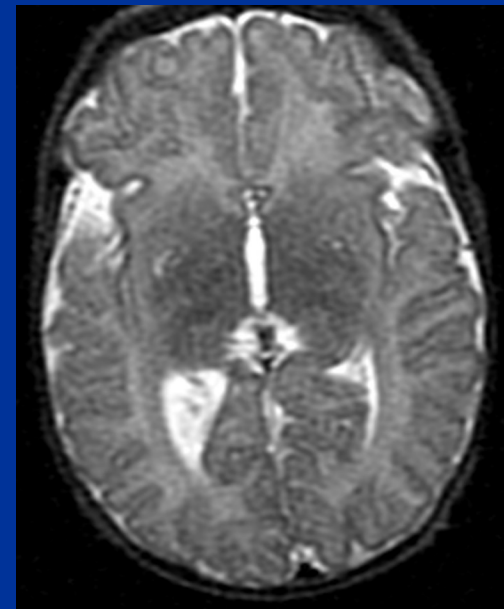
33w with unilateral ventriculomegaly



ss-FSE T2

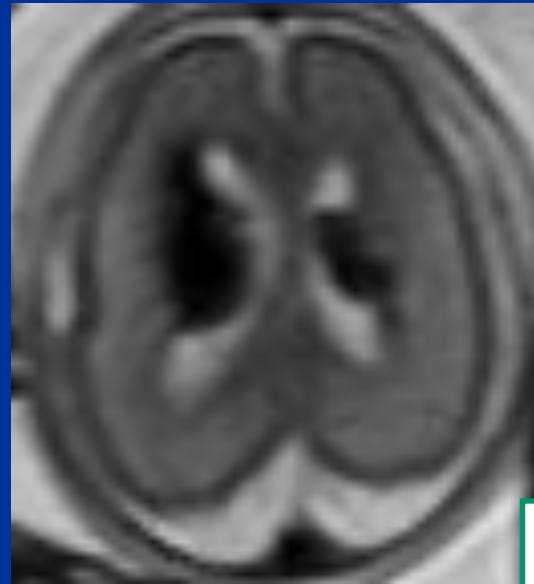


newborn

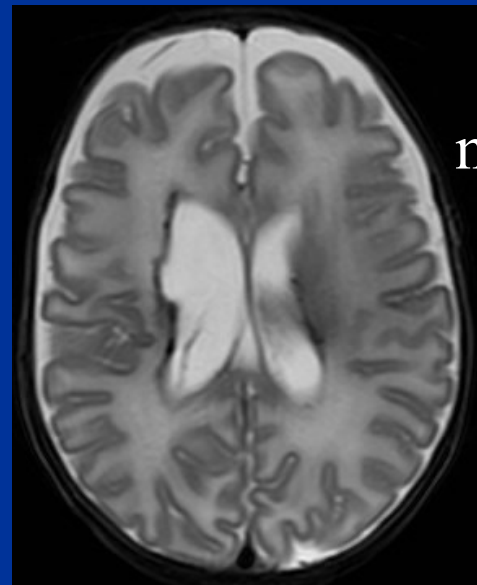


# IVH: parenchyma involvement evaluation

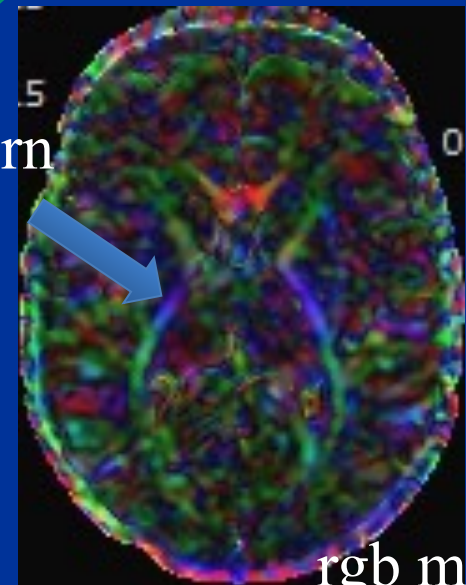
25w M  
MC, TTTS recipient:  
Periventricular  
hyperechoic,  
ascitis, polyhydramnios



early wallerian degeneration



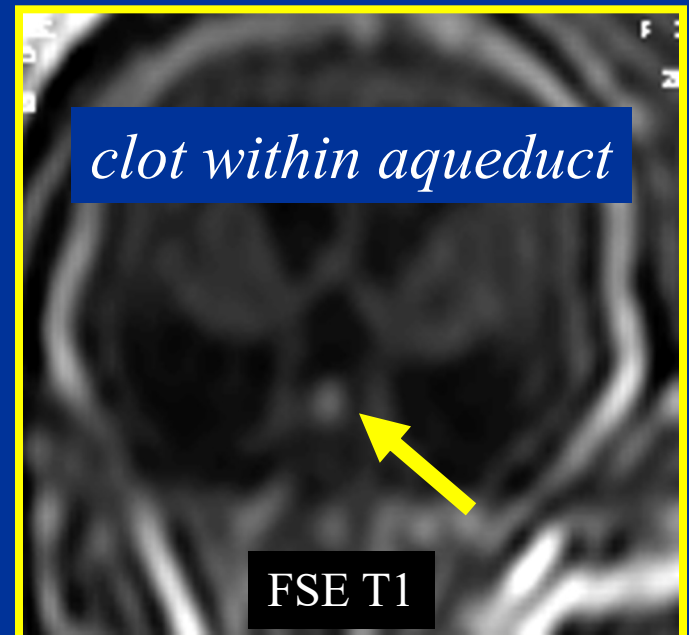
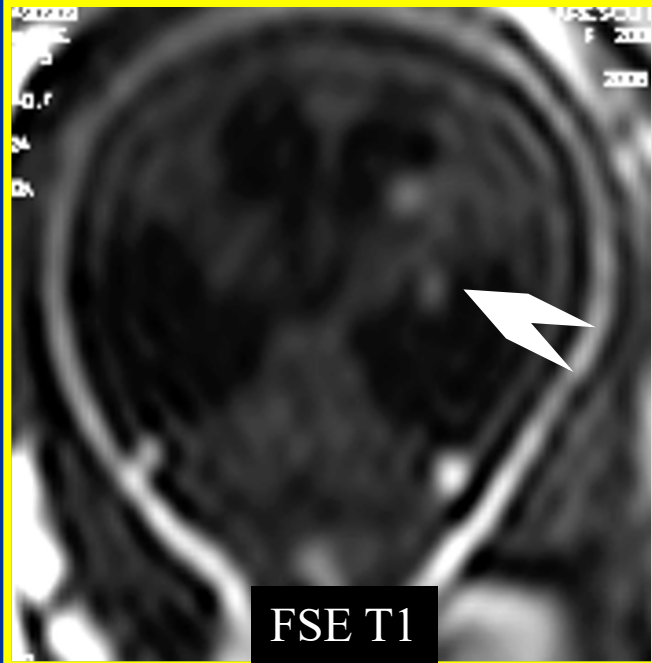
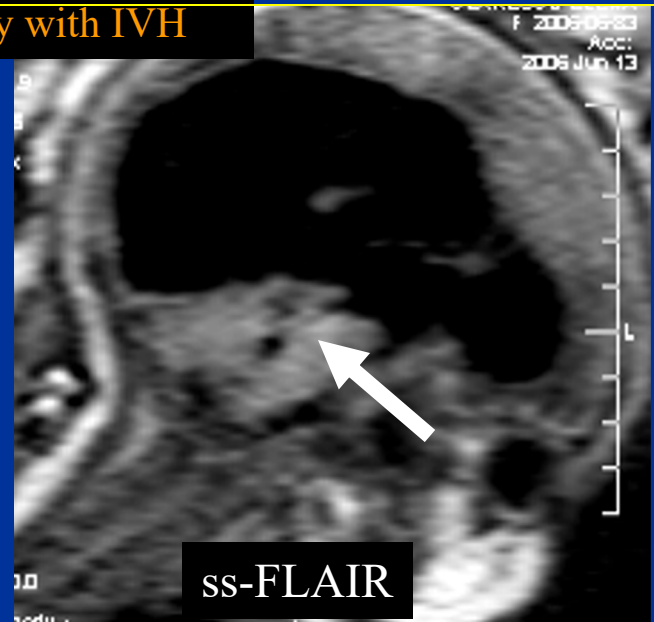
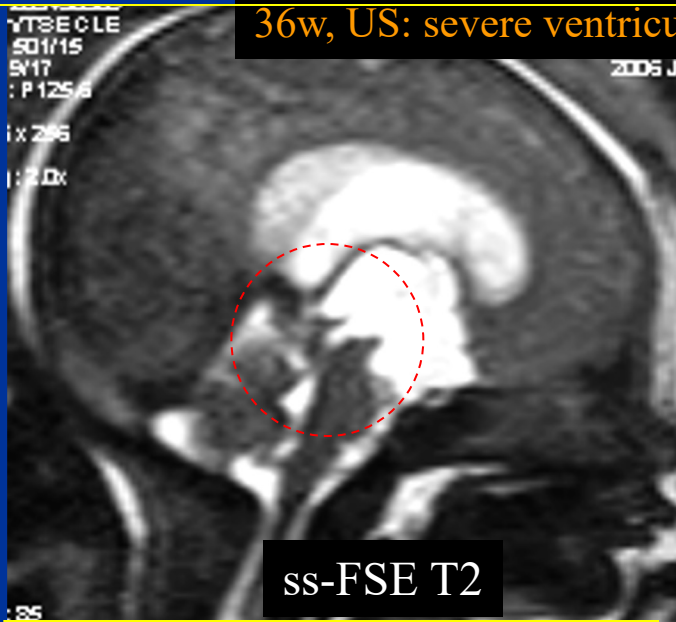
newborn



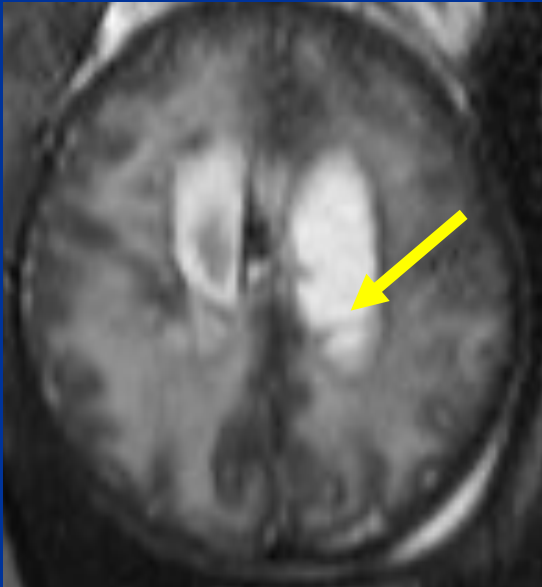
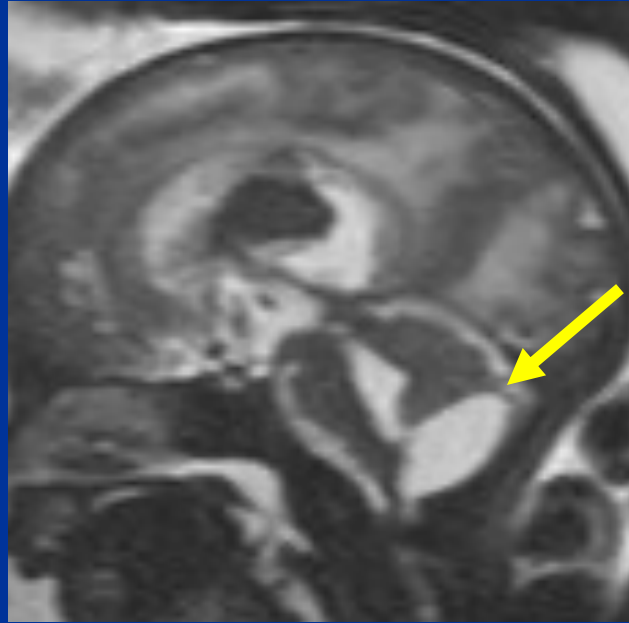
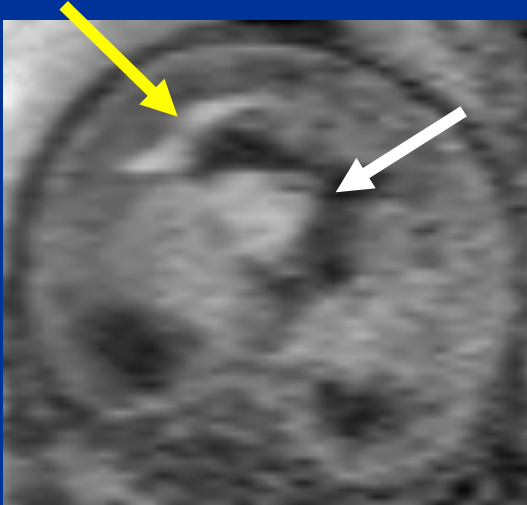
rgb map

# IVH with aqueductal obstruction and hydrocephalus

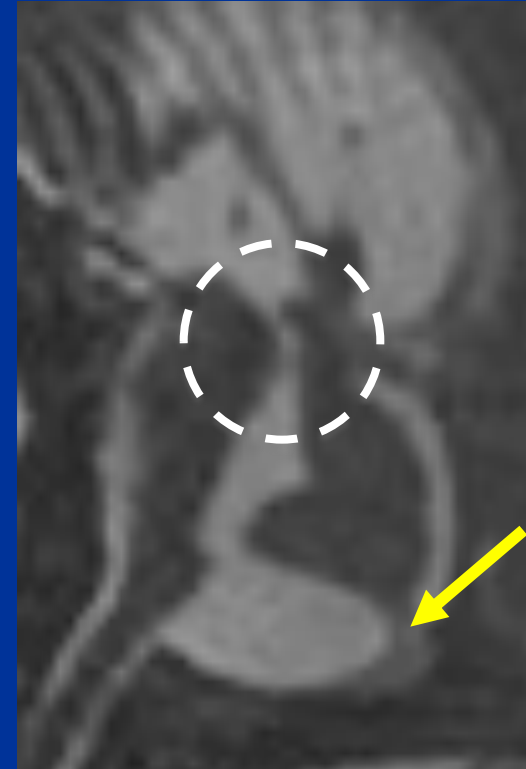
36w, US: severe ventriculomegaly with IVH



# IVH with ventriculomegaly, parenchyma involvement, basal cystem synechia-obstruction



36w M  
US: Ventriculomegaly,  
hyperechoic spots



# Fetal subdural hematoma

Hidden maternal autoimmune thrombocytopenia complicated by fetal subdural hematoma—case report and review of the literature

Livia Teresa Moreira Rios 2012

## MOTHER causes

- platelet or coagulation disorders,
- trauma,
- placental abruption,
- viral or bacterial infection
- amniocentesis,
- medications such as warfarin or cholestyramine,
- drugs such as cocaine.

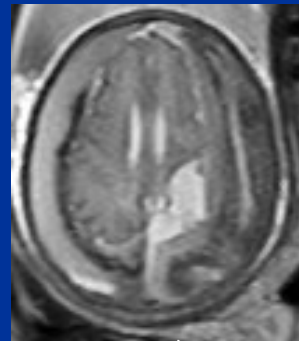
## FETUS causes

- congenital coagulopathy with factor V and factor X deficiency,
- fetomaternal hemorrhages, and
- fetal thrombocytopenias

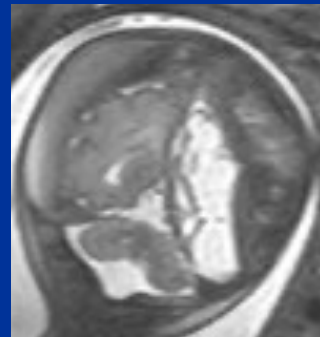
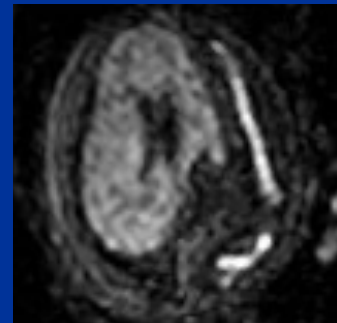
30w

- mother ematemesis 9dd before,
- fetal anemia
- coagulation factor II deficiency in the fetus

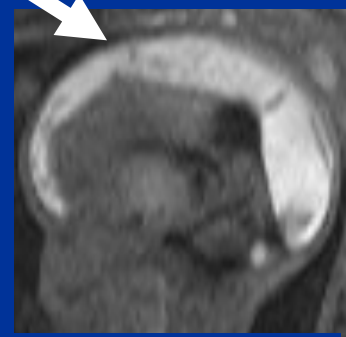
T2



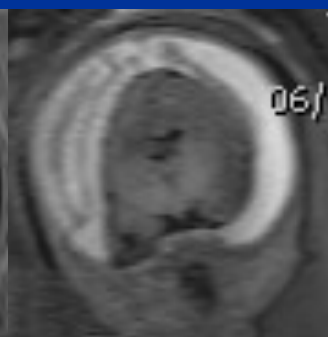
DWI



T2

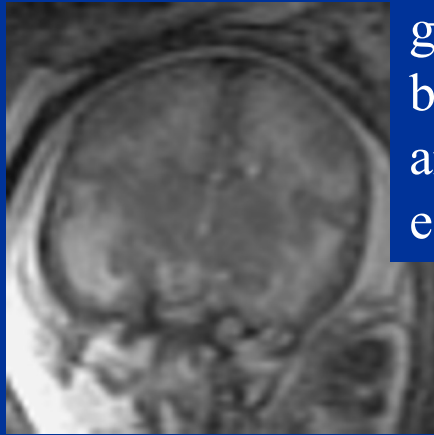


FLAIR

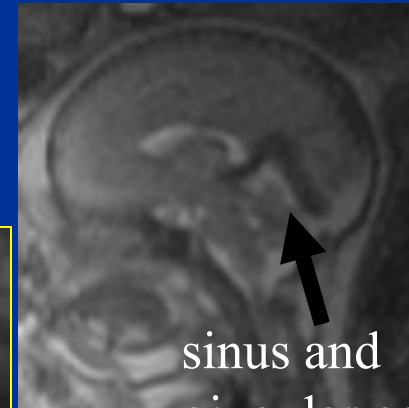


# Cerebral venous congestion and perivenular microhemorrhages

31w fetus, heart failure, severe hydrops.

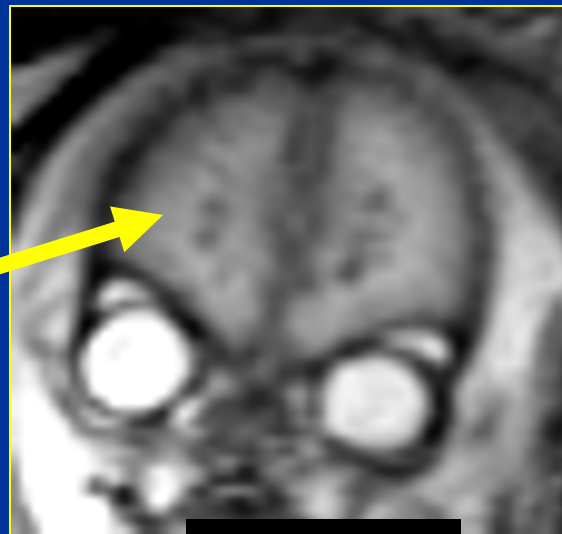


generalized  
brain swelling  
and interstitial  
edema

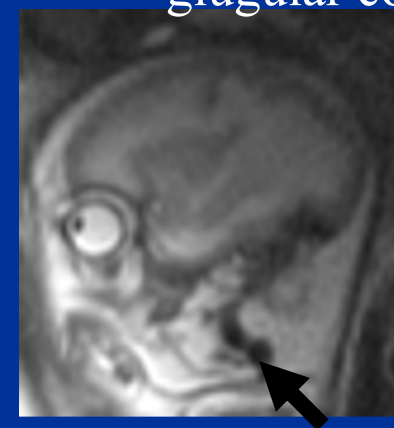


sinus and  
jugular congestion

*deep  
medullary  
veins*

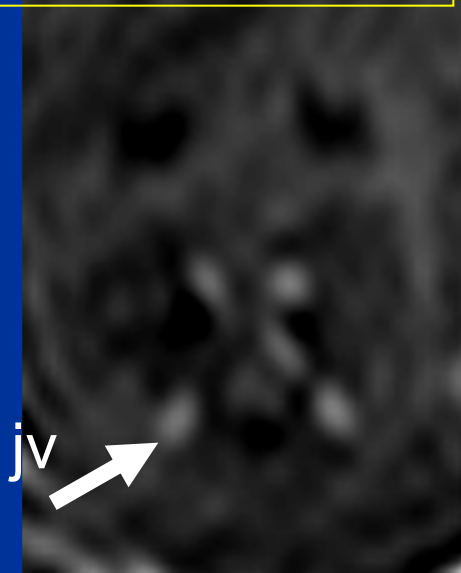
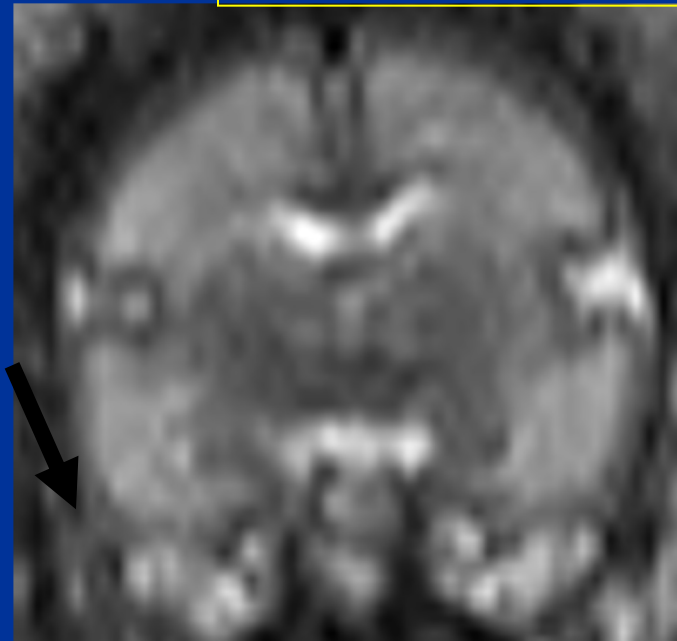


ss-FSE T2w

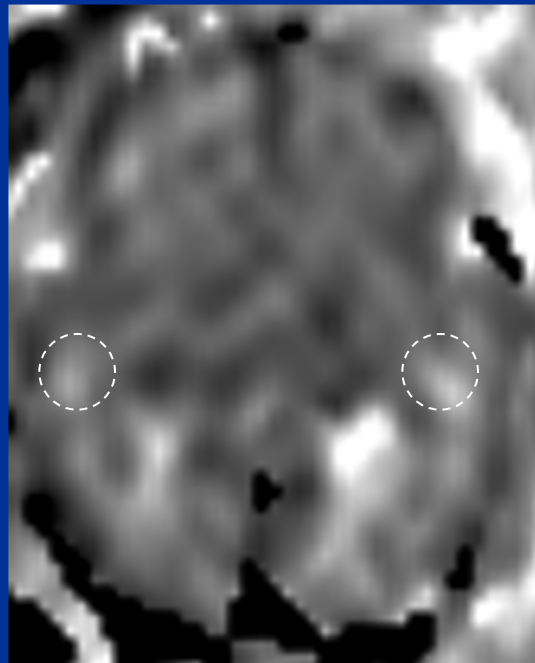


# Cerebral venous congestion and brain edema

27W, severe IUGR,  
anhydramnios,  
thorax hypoplasia,  
dead 2 days after MRI

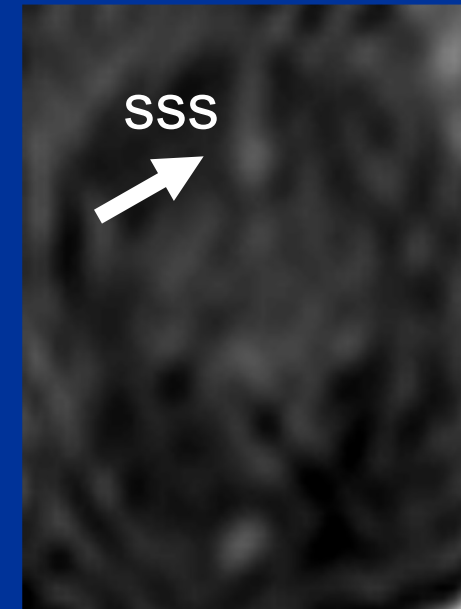


*venous  
sinus  
congestion*



ADC increased  
=  $2.3 \mu\text{m}^2/\text{msec}$

ADCmap



FSE-T1

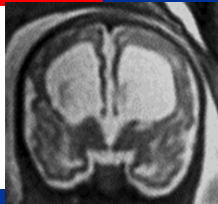
# congenital metabolic diseases

- Genetic diseases causing clastic lesions (parenchymal loss)
- Very rarerly diagnosed *in-utero* by fetal MRI, only sporadic case reports (mostly not specific signs)

## Pyruvate dehydrogenase deficiency

### A Review of Fetal Brain Pathology Acquired In Utero

D.J.A. Connolly. Neurographics  
2019 January



*Ultrasound Obstet Gynecol* 2002; 20: 616–619

## Prenatal diagnosis of hypoplasia of the corpus callosum in association with non-ketotic hyperglycinemia

A. PAUPE\*, L. BIDAT†, P. SONIGO‡, R. LENCLÉN\*, M. MOLHO\* and Y. VILLE†

\*Service de Pédiatrie et Médecine Néonatale, Centre Hospitalier Poissy-St Germain, Paris, France, †Service de Gynécologie-Obstétrique, Centre Hospitalier Poissy-St Germain, Paris, France and ‡Service de Radiologie, Hôpital des Enfants Malades, Paris, France

PRENATAL DIAGNOSIS

*Prenat Diagn* 2001; 21: 1053–1056.

DOI: 10.1002/pd.187

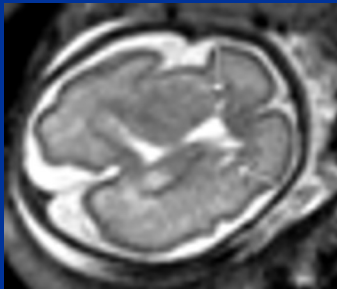
## Prenatal diagnosis of pyruvate dehydrogenase deficiency using magnetic resonance imaging

Julian N. Robinson<sup>1\*</sup>, Errol R. Norwitz<sup>2</sup>, Robert Mulkern<sup>3</sup>, Stephen A. Brown<sup>1</sup>, Frank Rybicki<sup>4</sup> and Clare M. C. Tempny<sup>4</sup>

*Molecular Genetics and Metabolism* 102, 2011, 149–152

## Fatal infantile lactic acidosis and a novel homozygous mutation in the SUCLG1 gene: A mitochondrial DNA depletion disorder

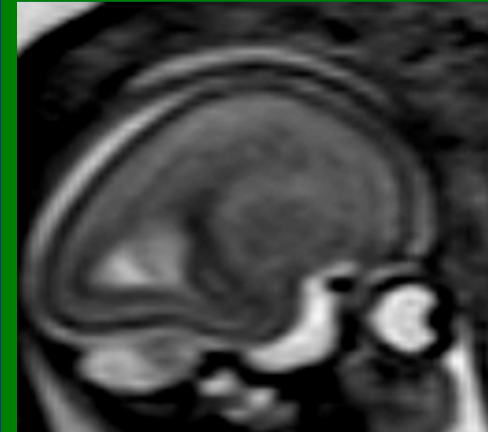
•Linda M. Randolph et. Al.



# Glutaric aciduria type 1

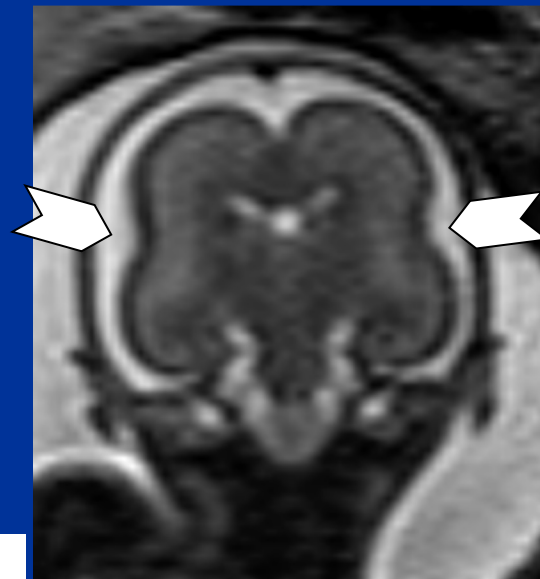


22 w F,  
parents 2nd degr.  
cousins.

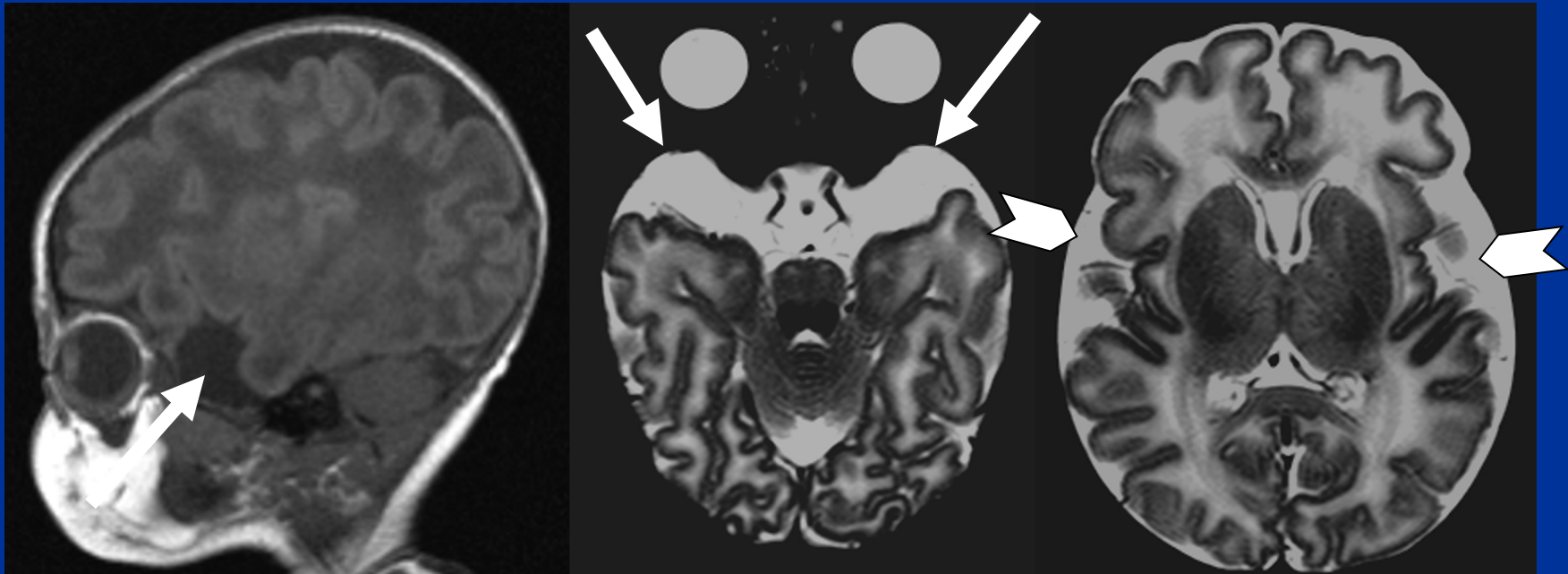


normal control

*temporal lobe tip  
volume reduction*



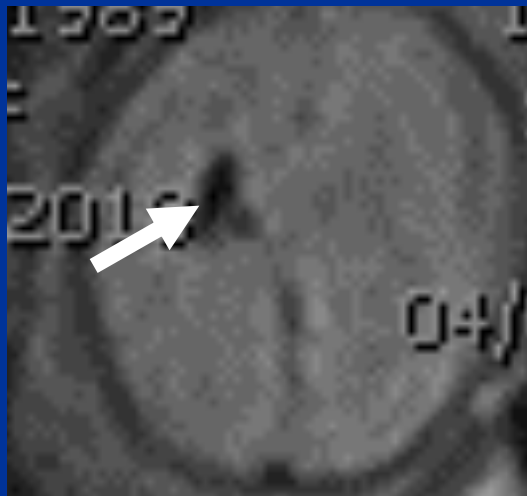
# *Glutaric aciduria type 1*



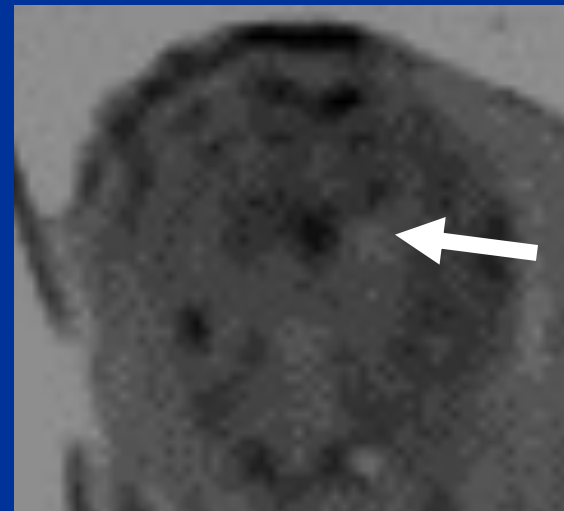
neonatal MRI

24w, M  
ventriculomegaly

# D-2 hydroxyglutaric aciduria



GRE T2\*



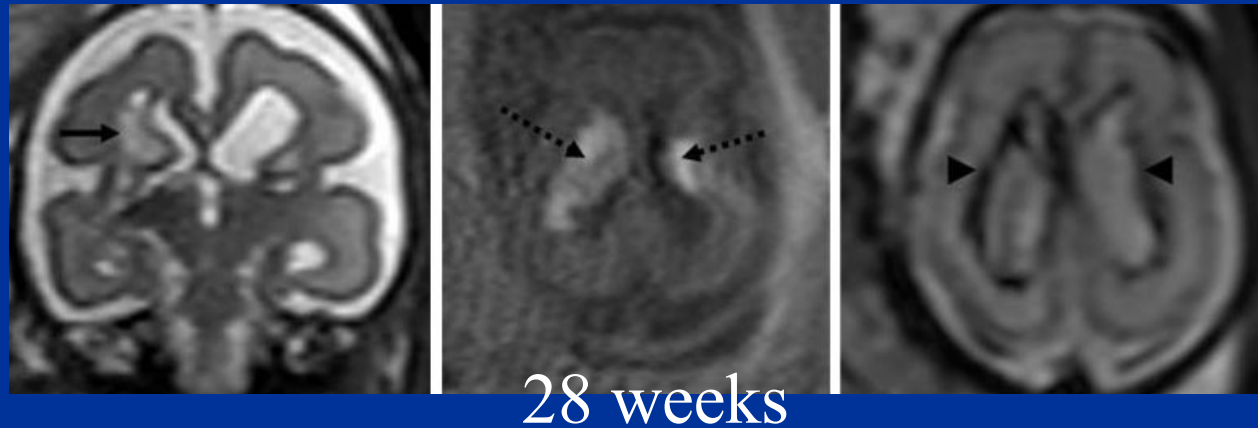
T1

# Differential diagnosis with rare “pseudoclastic” genetic conditions - 1

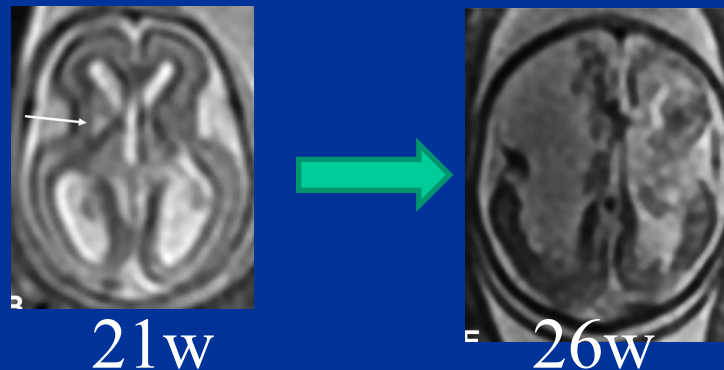
**Fetal intracerebral hemorrhage and COL4A1 mutation: promise and uncertainty**

C. Garel et Al. *Ultrasound Obstet Gynecol* 2013

COL4A1 gene for  
alfa1 chain of collagen  
type IV of basal  
membrane (intima) of  
vessels



**A Review of Fetal Brain  
Pathology Acquired In Utero**  
D.J.A. Connolly. *Neurographics*  
2019 January



COL4A1 «double hit» lesions

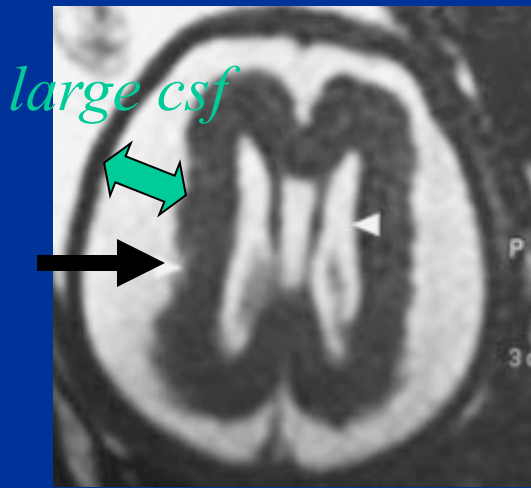
# Differential diagnosis with rare “pseudoclastic” genetic conditions - 2

• 2008 Wiley-Liss, Inc.

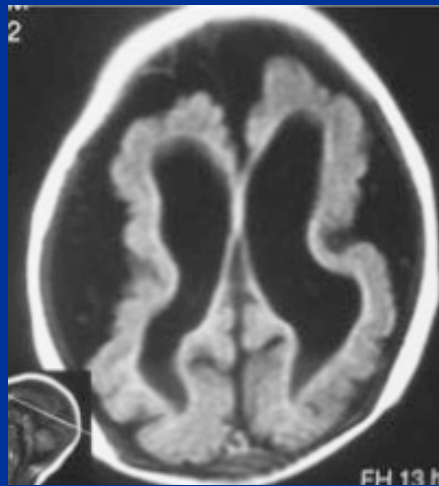
American Journal of Medical Genetics Part A 146A:2929–2936 (2008)

## Clinical Report Microcephaly, Malformation of Brain Development and Intracranial Calcification in Sibs: **Pseudo-TORCH** or a New Syndrome

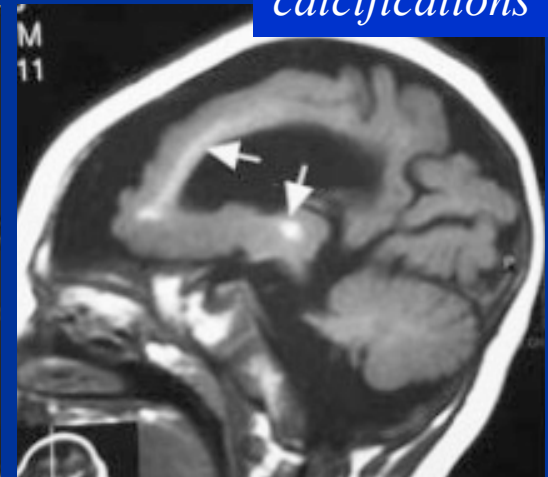
Ghada M.H. Abdel-Salam,<sup>1\*</sup> Maha S. Zaki,<sup>1</sup> Sahar N. Saleem,<sup>2</sup> and Khaled R. Gaber<sup>3</sup>



fetus



newborn

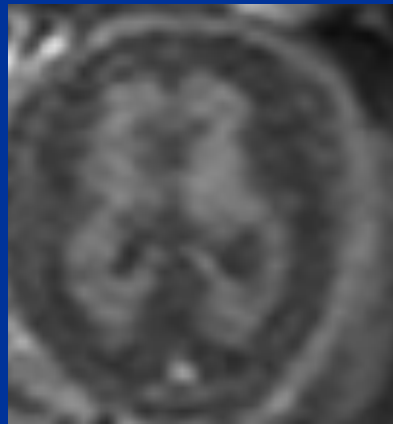
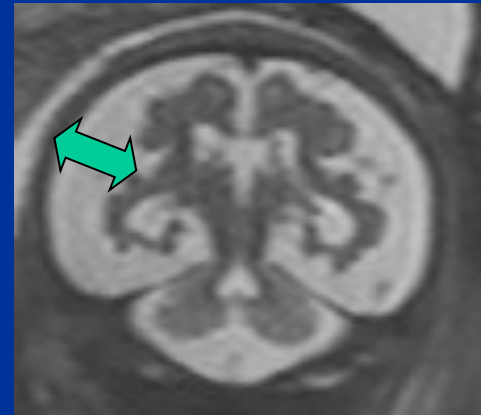
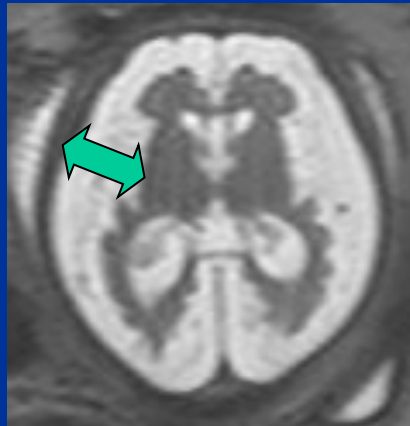


calcifications

# Differential diagnosis with rare *“pseudoclastic”* genetic conditions - 3

29w, severe microcephaly also in previous pregnancy

- abnormal apoptosis ?
- intrauterine neurodegeneration?

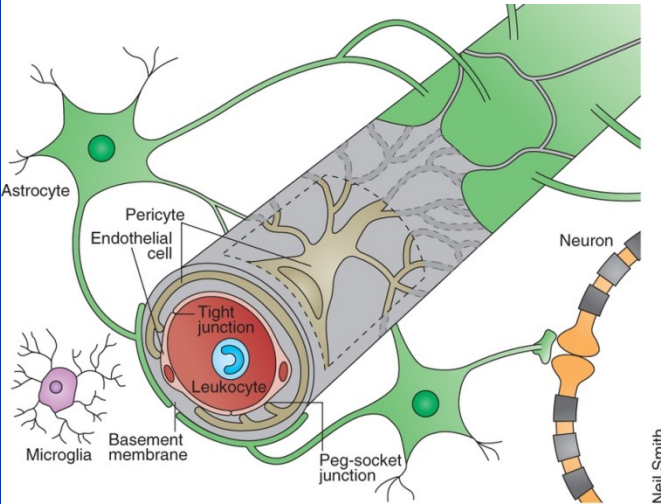


*NO T1-w focal hyperintensities*

# "pseudo-TORCH: gene based malformative-clastic microencephalies"

*Hypothesis: vascular mediated disruption of cell proliferation, migration and organization*

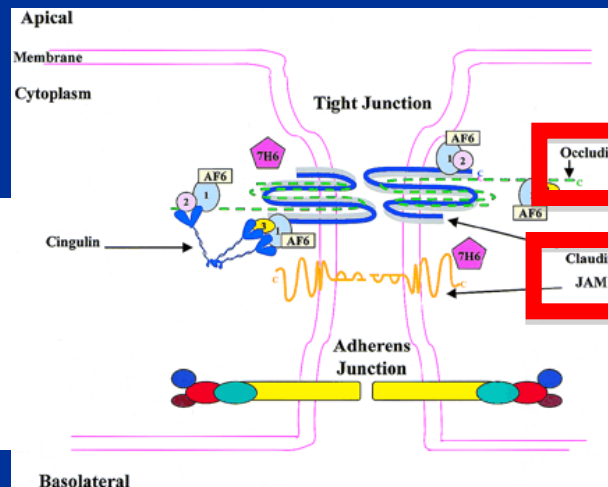
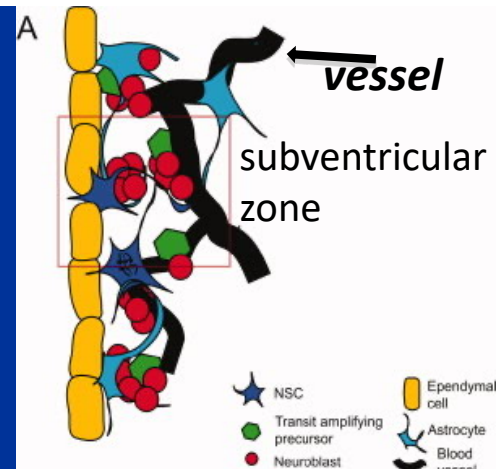
*Nature Medicine 2013*  
 Development, maintenance and disruption of the blood-brain barrier  
 Birgit Obermeier et Al..



Inflammatory pain alters blood-brain barrier permeability and tight junctional protein expression  
 J. D. Huber et Al..  
 American Journal of Physiology - Heart and Circulatory Physiology 2001

Subventricular Zone:  
 actively dividing precursors reside next to blood vessels.

[Developmental Neurobiology](#) 2011

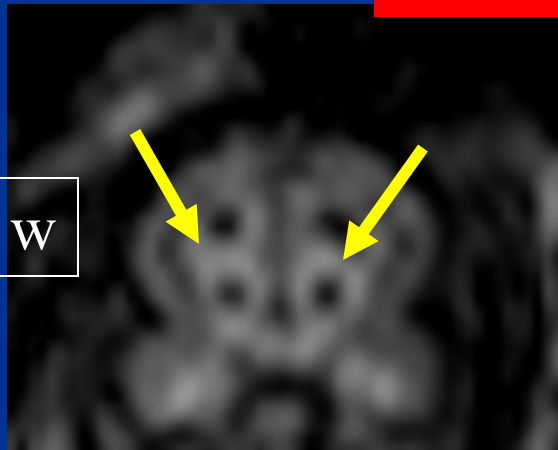


**Tight junction proteins:**  
claudins,  
occludins and  
JAMs

# Differential diagnosis with rare *“pseudoclastic”* genetic conditions - 4

cavitations-cysts

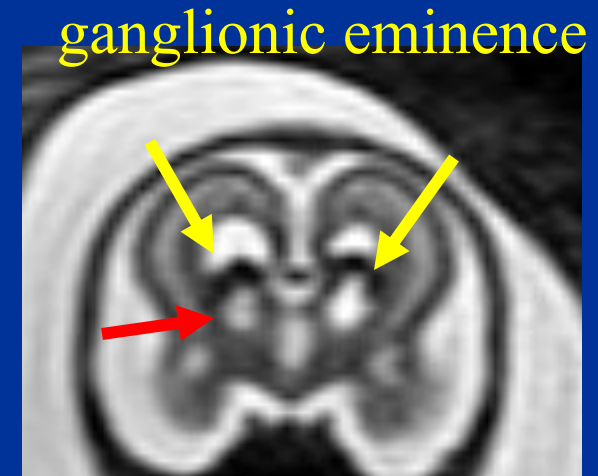
Righini A et al.. AJNR, in press



DWI



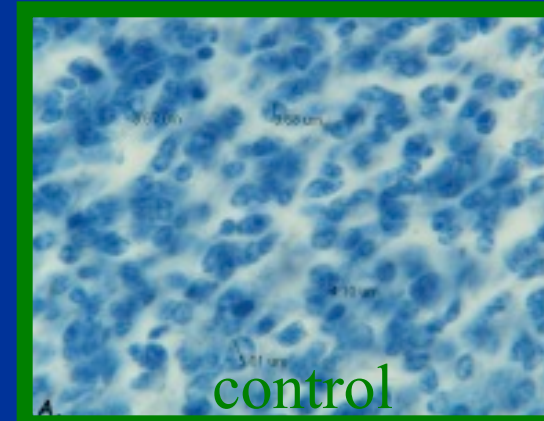
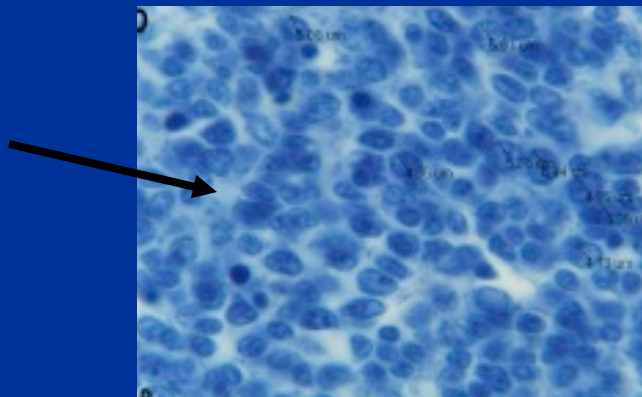
ADC



T2

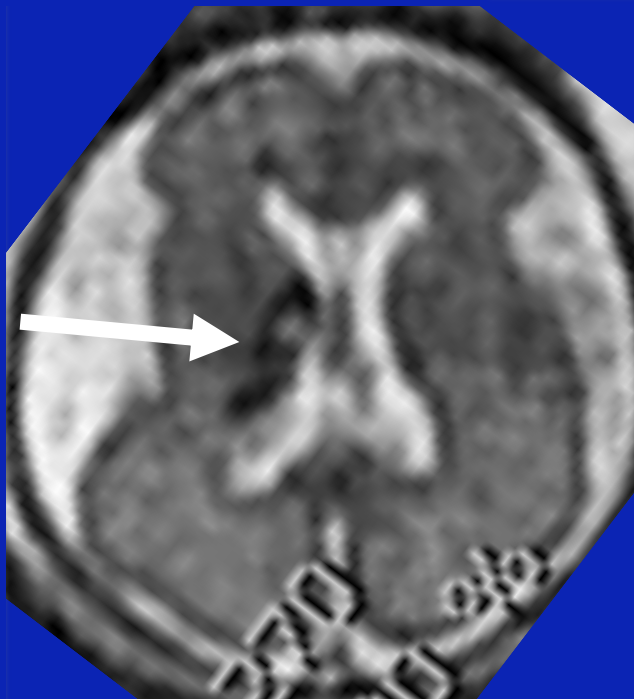
22 w

ganglionic eminence



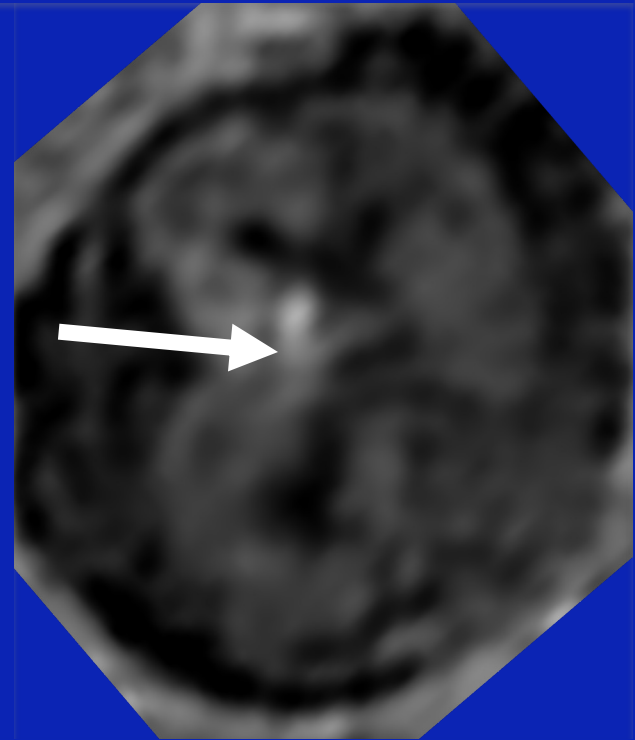
Differential diagnosis with germinal matrix haemorrhage and cysts in Ganglionic Eminence region

T2



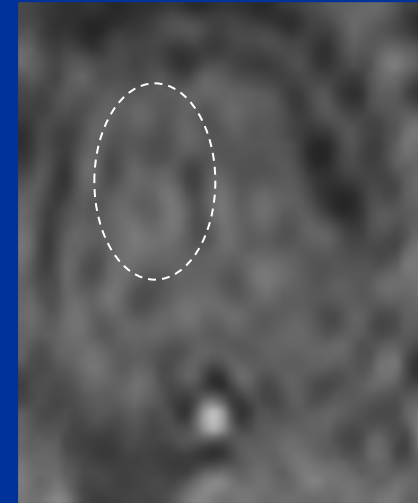
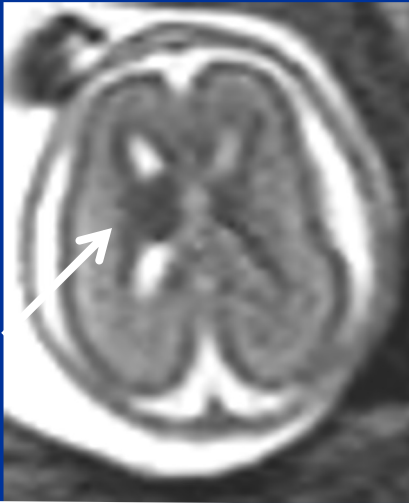
26 w

T1



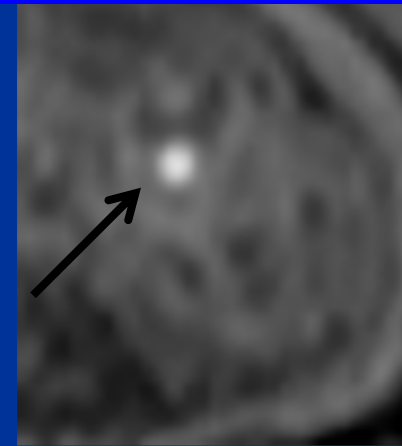
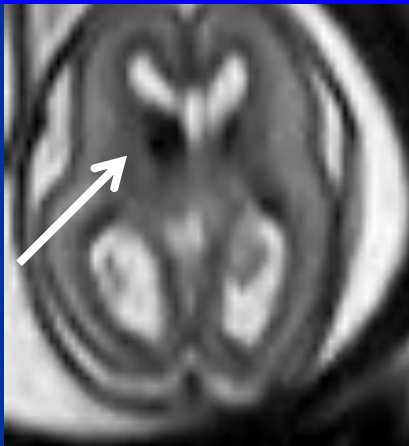
T1-w

# Ganglionic Eminence volume increase-hypertrophy



T1-w

Differential diagnosis with germinal matrix haemorrhage in Ganglionic Eminence region



T1-w

*thank you*