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Proyecto ECHO ASSIST- Zika

19 Diciembre 2018

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University Research Co., LLC

Convulsiones y complicaciones neurológicas en recién nacidos y lactantes: Sindrome Congénito de Zika

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Objectivos de Aprendizaje

Después de esta presentación, Ud. debería ser capaz de:

- **Entender lo que se sabe sobre convulsiones y otras complicaciones neurológicas en relación a la infección congénita con el virus de Zika**
- **Discutir las recomendaciones de manejo de los recién nacidos y lactantes con convulsiones y otras manifestaciones neurológicas.**

Comparación de los síntomas en enfermedades transmitidas por el mosquito Aedes

SINTOMAS	Dengue	Chikunguya	Zika
Fiebre	++++	+++	**+++**
Mialgia/artralgia	+++	++++	++
Edema de extremidades	0	0	**++**
Exantema	++	++	**+++**
Dolor retro-orbital	++	+	++
Conjuntivitis	0	+	**+++**
Linfadenopatías	++	++	+
Hepatomegalia	0	+++	0
Leucopenia/trombocitopenia	+++	+++	0
Hemorragia	+	0	0

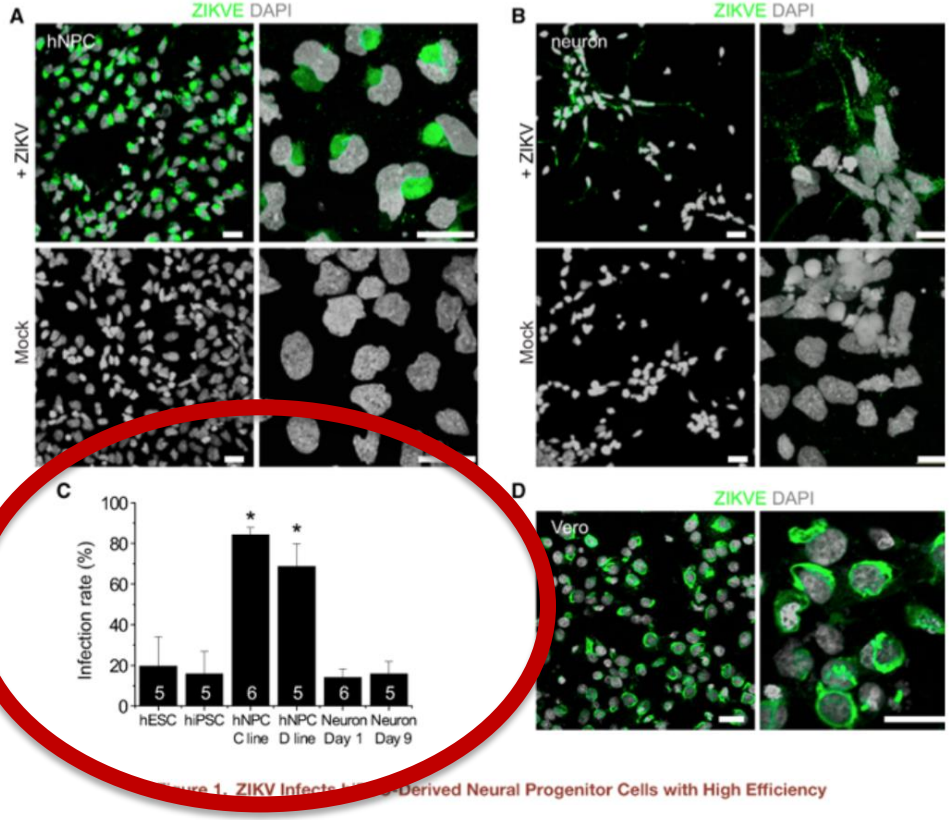
CDC, MODIFIED BY ALCY TORRES, 2018

SINDROME CONGENITO DE ZIKA 1

Signos y síntomas	Grupo 1 MIC	Grupo 2 Normal
Enfermedad Materna Viral	38/56 (68%)	7/9 (78%)
1st trimestre 2nd trimestre 3rd trimestre	26/56 (46%) 09/56 (15%) 02/56 (4%)	3/9 (33%) 4/9 (44%) 0
Pruebas Serológicas ZIKA		
Pruebas Serológicas y genéticas Positivos resultados ZIKA	10/57 (18%) 10/10 (100%)	7/9 (78%) 2/9 (22%)
Edad Gestacional		
Término Prematuros	50/57 (88%) 07/57 (12%)	

Dobyns and the Brazilian Zika group, 2016

ZIKA en las neuronas



Derived Neural Progenitor Cells with High Efficiency

Cell Stem Cell
Brief Report
CellPress

Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth

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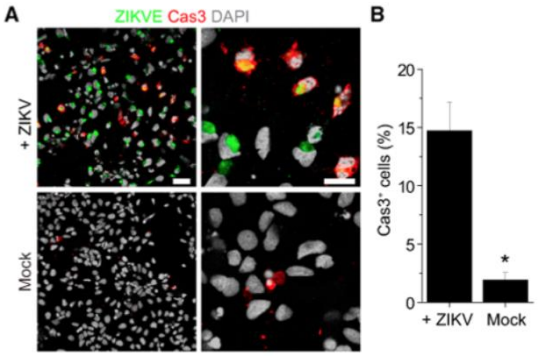
SUMMARY

The suspected link between infection by Zika virus (ZIKV), a re-emerging flavivirus, and microcephaly is an urgent global health concern. The direct target cells of ZIKV in the developing human fetus are not clear. Here we show that a strain of the ZIKV, MR766, serially passaged in monkey and mosquito cells efficiently infects human neural progenitor cells (hNPCs) derived from induced pluripotent stem cells. Infected hNPCs further release infectious ZIKV particles. Importantly, ZIKV infection increases cell death and dysregulates cell-cycle progression, resulting in attenuated hNPC growth. Global gene expression analysis of infected hNPCs reveals transcriptional dysregulation, notably of cell cycle related pathways. Our results identify a target. In addition, mental model system mechanism of ZIKV and provide a platform pounds.

Zika virus (ZIKV), a mosquito be circulating in 26 countries the Caribbean (Petersen et can often be asymptomatic mounting concern are and newborn microcephaly tions, such as Guillain-Barré The World Health Organization gency of International Concern et al., 2016). ZIKV infection

major transmission route (Hamel et al., 2015). ZIKV was detected in the amniotic fluid of two pregnant women whose fetuses had been diagnosed with microcephaly (Calvet et al., 2016), suggesting that ZIKV can cross the placental barrier. ZIKV was also found in microcephalic fetal brain tissue (Mlakar et al., 2016). Because so little is known about direct cell targets and mechanisms of ZIKV, and because access to fetal human brain tissue is limited, there is an urgent need to develop a new strategy to determine whether there is a causal relationship between ZIKV infection and microcephaly. Here we used human induced pluripotent stem cells (hiPSCs) as an in vitro model to investigate whether ZIKV directly infects human neural cells and the nature of its impact.

We obtained a ZIKV stock from the infected rhesus *Macaca* cell line LLC-MK2. We passaged the virus in the mosquito C6/C36 cell line and titered collected ZIKV on Vero cells, an interferon-deficient monkey cell line commonly used to titer viruses



Neurons derived from radial glial cells establish radial units in neocortex

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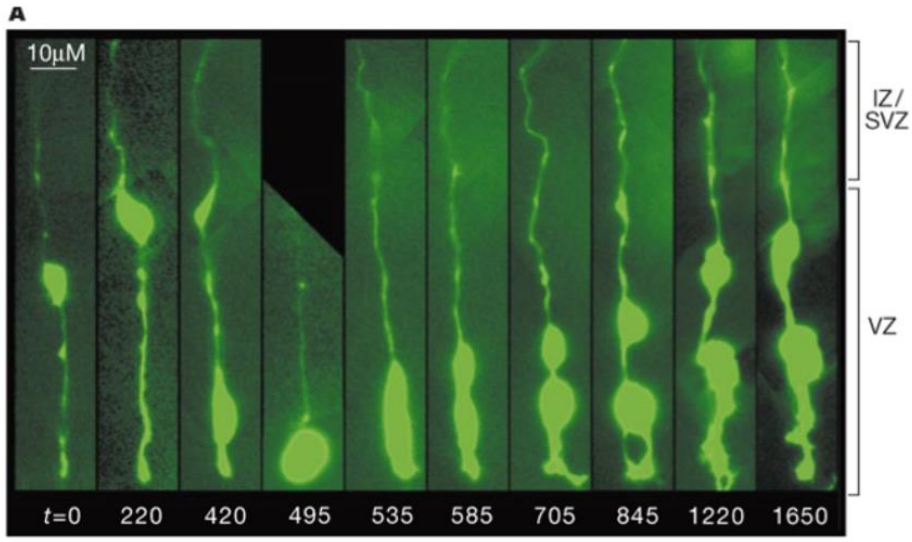

alone. Hence, these findings not only substantiate the fact of mosaic brain evolution, but begin to unravel its various causes. Finally, the observed evolutionary radiations in brain organization appear to coincide with such fundamental dimensions of cognition as motor planning, perceptual representation, and spatio-temporal memory. Hence, rather than a single evolutionary progression in general 'intelligence' across mammals, different dimensions of 'intelligence' appear to have evolved independently in different lineages. □

Methods

We introduce here a hypothesis-free multivariate morphometric approach[37] to the comparative study of quantitative data on the mammalian brain. Rather than using inferential statistics to test a priori hypotheses about the data, we explore the multi-dimensional structure of the data in all its intricate detail using descriptive multivariate statistics[38] and data visualization[39]. Hence it is robust to phylogenetic dependencies between specimens.

We apply this approach to the full complement (921 specimens) of Stephan's original measurements on the volumes of the 11 major divisions of the brain stem and forebrain in 363 species of primates, insectivores, bats, tree-shrews and elephant-shrews. The data include the raw volumes of: medulla (+ reticular formation), cerebellum (+ brachium, nuclei pontis), midbrain (– reticular nucleus), diencephalon, olfactory bulb, palaeocortex (+ amygdala), septum, hippocampus, schizocortex (entorhinal, perirhinal and presubicular cortices), and neocortex (isocortical grey + underlying white matter)[10].

In order to obtain measures that are more sensitive to variations in the functional, systemic interdependence of these brain parts, we reorganized the data within each specimen to reflect variations in major input–output proportions[26]. We identified two fundamental sets of such projections that vary between taxa: peripheral projections associated with varying body size, and, thus to some extent with the size of the medulla[27], and internal projections associated with variations in the size of the neocortex[5,26]. The size of each brain part was therefore described relative to medulla and neocortex within the same specimen. This resulted in 19 different brain structure proportions across different developmental growth fields[26]. Although these proportions were derived mathematically, they in fact represent empirically measurable properties that are intrinsic to each specimen.

After univariate and bivariate examination of both the raw and the transformed data sets, a principal components analysis was applied to the correlation matrix of the functionally rearranged brain data. Only the first three components were retained for further analysis, reducing the dimensionality of the data space from 19 to 3, while preserving 85% of its total variance. Phylogenetic and lifestyle associations among species, within the data subspace spanned by these first three principal components, were investigated interactively by dynamic three-dimensional computer representations with data points rendered as colour-coded spheres with coloured highlights (Figs 1 to 3). Varimax rotation aligned these components with the directions of major dispersion for the three largest mammalian orders. This allowed identification through biplots (Fig. 4) of the associations between the variables that contributed most to those dispersions. Biplots combine graphical displays of the relationships between data points and those between variables into a single plot[38], thus showing the interrelationships between the two.

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Neurons derived from radial glial cells establish radial units in neocortex

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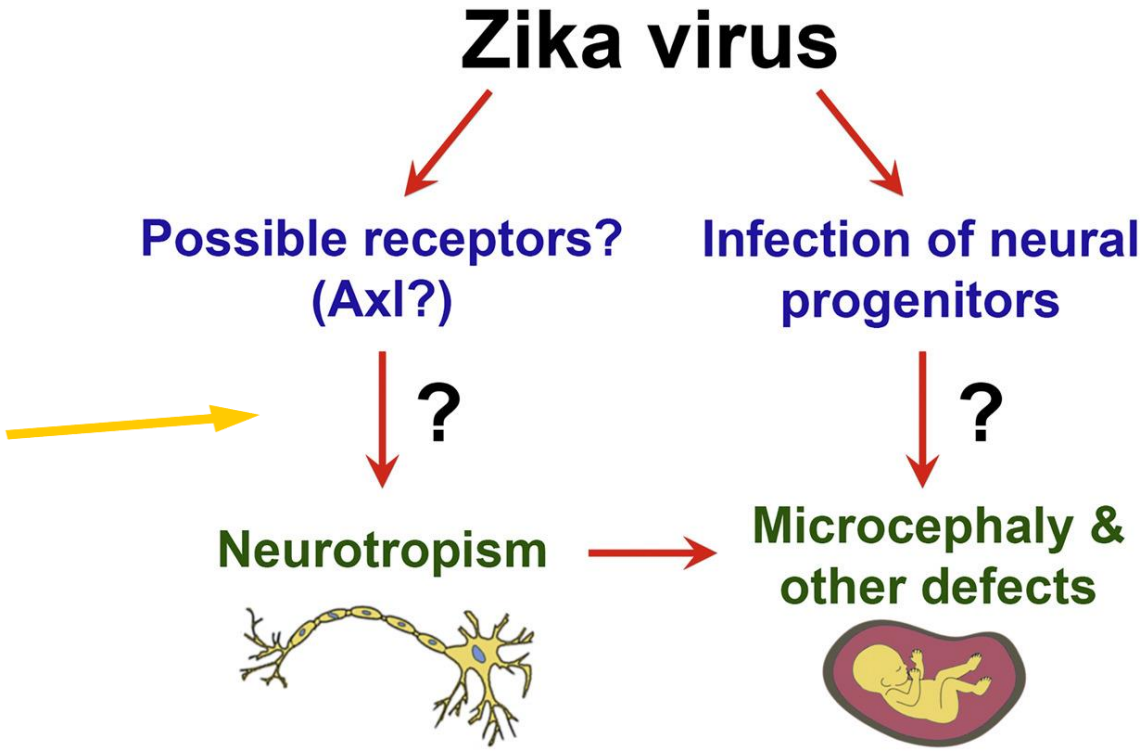
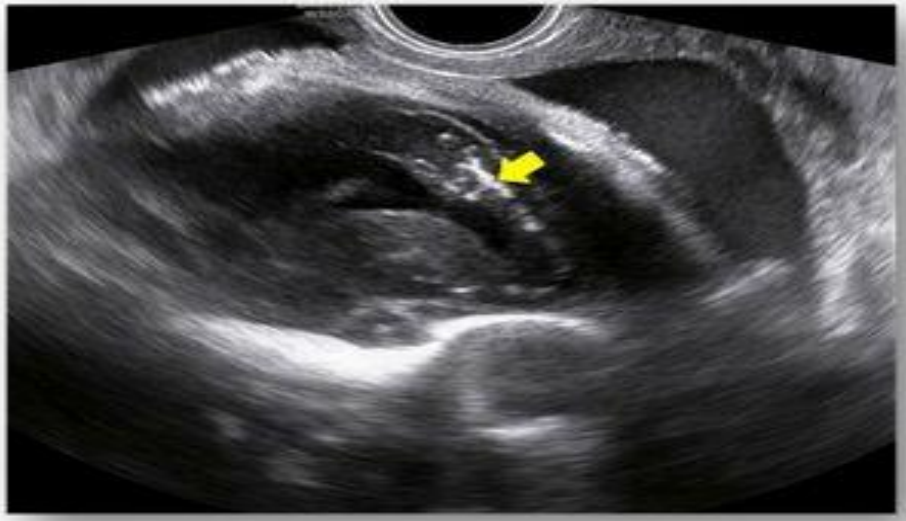
The neocortex of the adult brain consists of neurons and glia that are generated by precursor cells of the embryonic ventricular zone. In general, glia are generated after neurons during development[1], but radial glia are an exception to this rule. Radial glia are generated before neurogenesis and guide neuronal migration[2]. Radial glia are mitotically active throughout neurogenesis[3], and disappear or become astrocytes when neuronal migration is complete[4,5]. Although the lineage relationships of cortical neurons and glia have been explored[6,7], the clonal relationship of radial glia to other cortical cells remains unknown. It has been suggested that radial glia may be neuronal precursors[5,8–10], but this has not been demonstrated *in vivo*. We have used a retroviral vector encoding enhanced green fluorescent protein to label precursor cells *in vivo* and have examined clones 1–3 days later using morphological, immunohistochemical and electrophysiological techniques. Here we show that clones consist of mitotic radial glia and postmitotic neurons, and that neurons migrate along clonally related radial glia. Time-lapse images show that proliferative radial glia generate neurons. Our results support the concept that a lineage relationship between neurons and proliferative radial glia may underlie the radial organization of neocortex.

Neurons in mammalian neocortex are aligned in columnar or radial units that receive similar inputs and serve similar functions[11]. The 'radial unit hypothesis' of neocortical development proposes that functional radial units are established by the proliferation of precursor cells in the embryonic ventricular zone, giving rise to



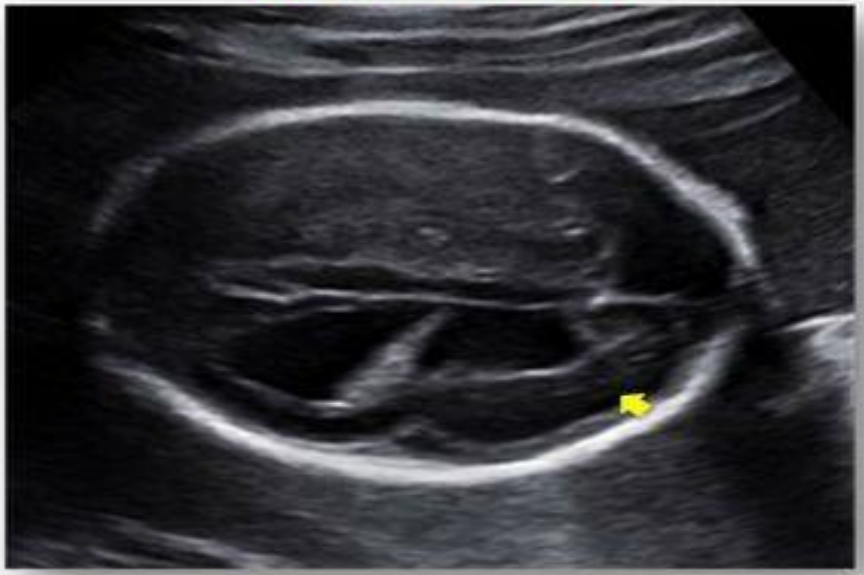
Toll-like receptor 3a

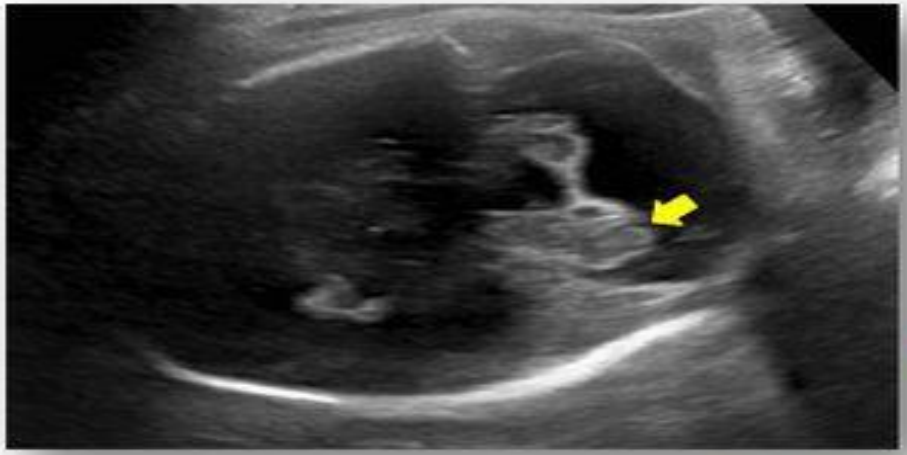
Síndrome ZIKV congênita



Calcificações intracranianas

Hidrocefalia

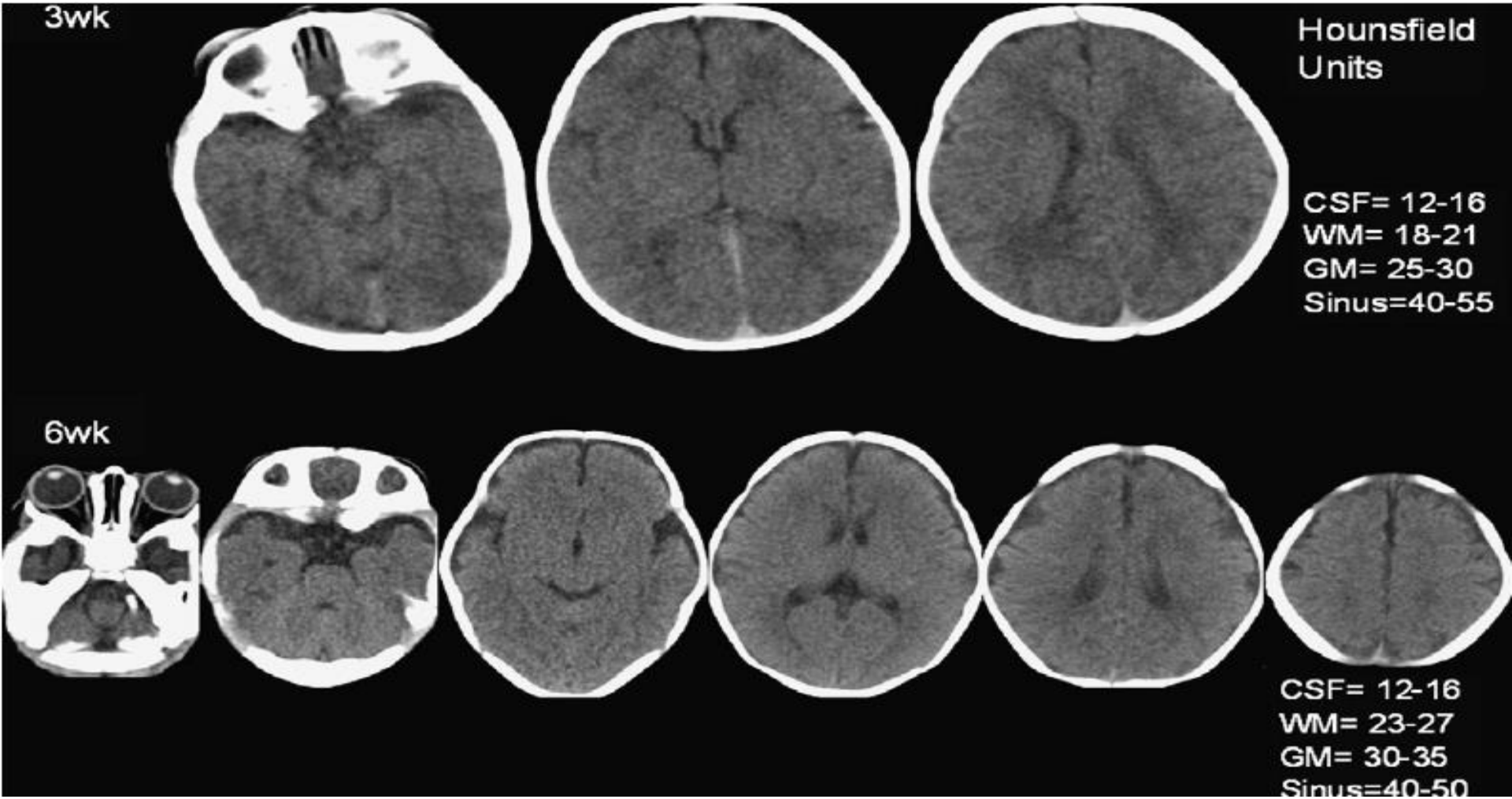




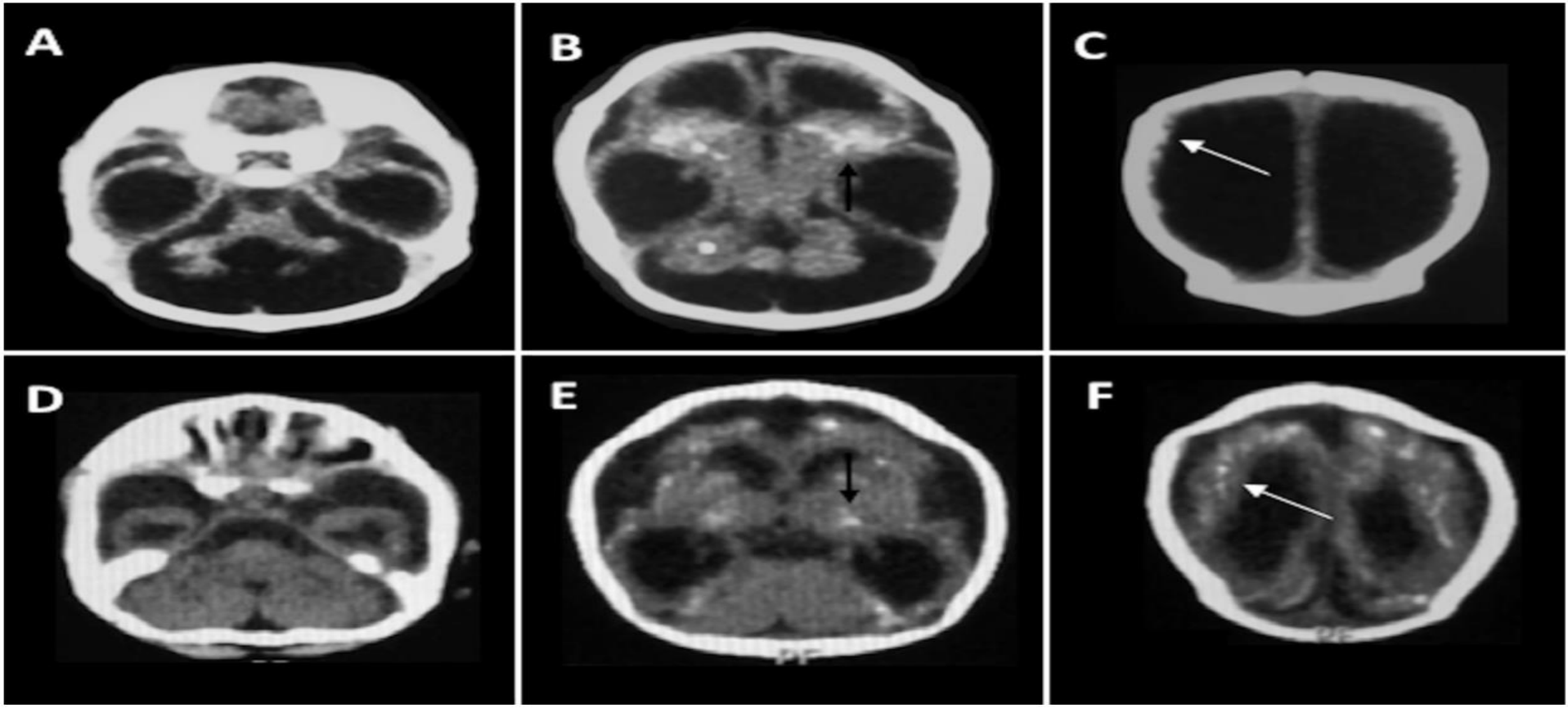
Cerebelo/Vérmis hipoplásicos

Adriana Melo, Campina Grande, PB, 2016

TOMOGRAFIA AXIAL COMPUTARIZADA



SINDROME CONGENITO DE ZIKA TAC

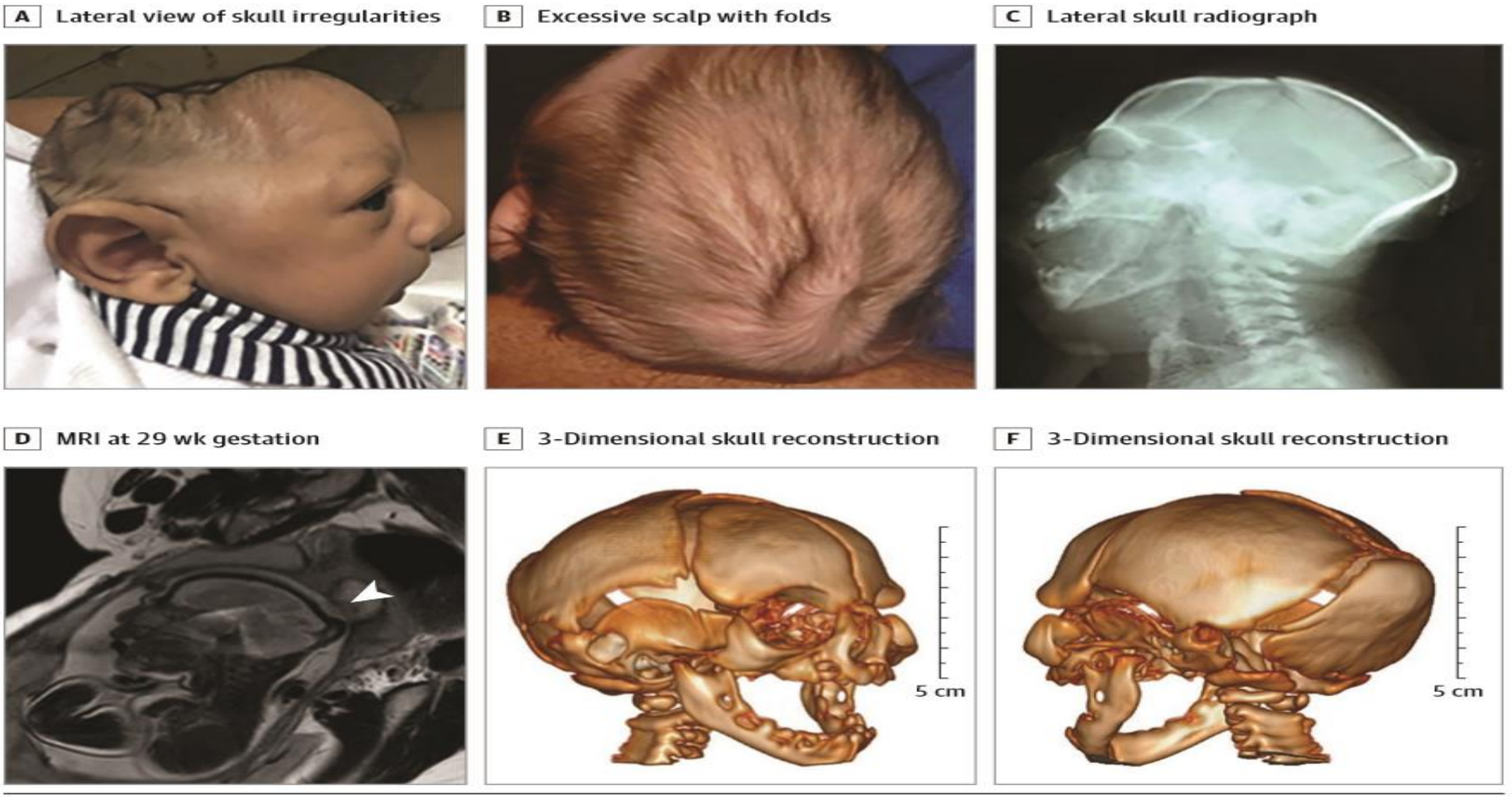


Sequencia de destrucción cerebral fetal

- **Descrita por primera vez 1984 pero identificada anteriormente**
- **La destrucción cerebral resulta en el colapso de los huesos del cráneo, microcefalia, arrugas del cuero cabelludo y daño neurológico**

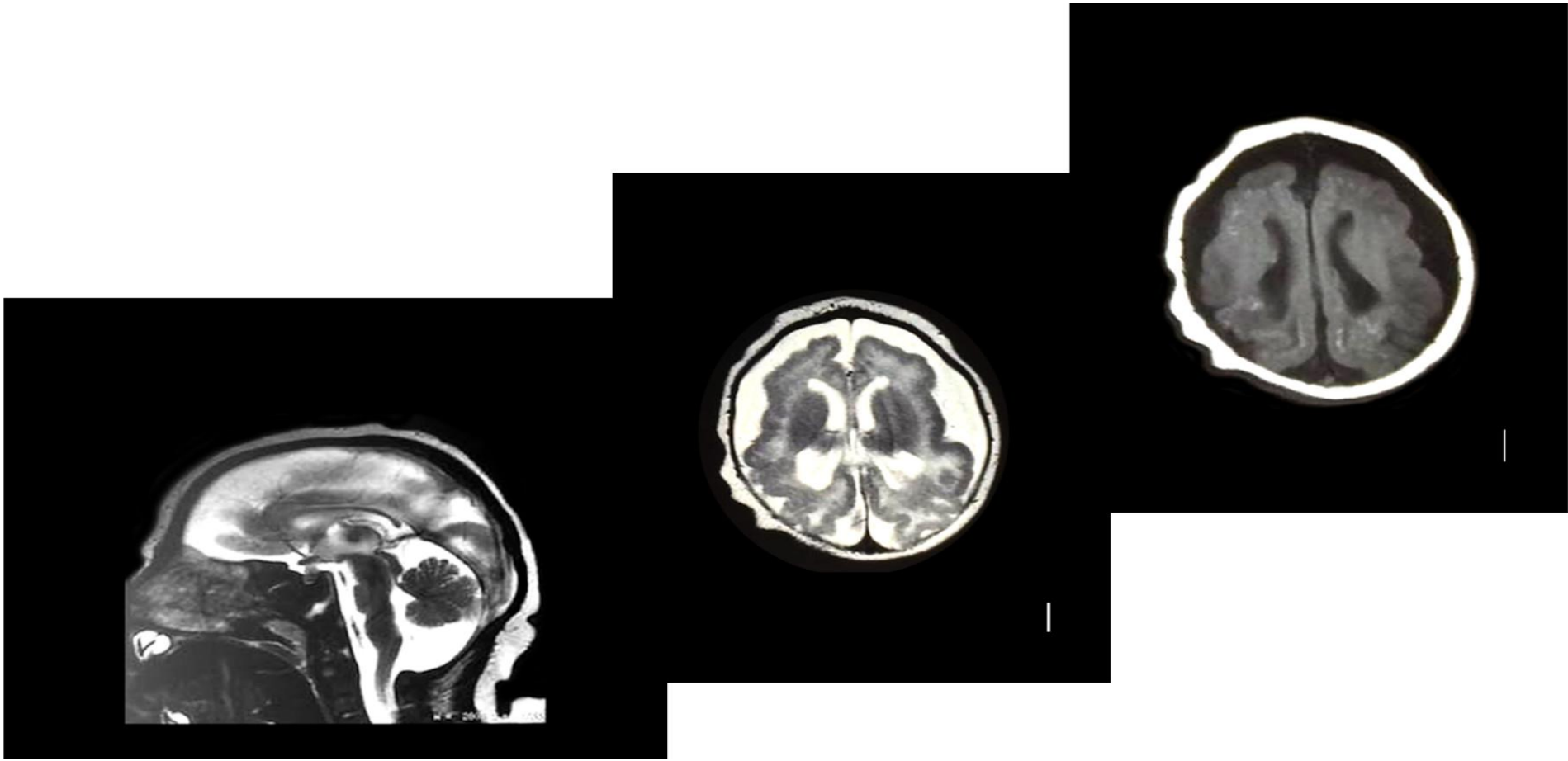
- **Russell LJ, Weaver DD, Bull MJ, Weinbaum M.**

  Am J Med Genet. 1984 Feb;17(2):509-21.



JAMA Pediatrics: November 3, 2016. doi:10.1001/jamapediatrics.2016.3982

Zika-RMN



SINDROME CONGENITO DE ZIKA 2

Signos y síntomas	Group 1 MIC	Group 2 Normal
Crecimiento y perímetro cefálico		
MIC –2 to –3 SD MIC debajo –3 SD RCIU	PC PROMEDIO -4.13 +/- 1.4 SD	0/9 0/9 0/9
Anormalidades Neurológicas		
Espasticidad Irritabilidad severa y/o temblor Artrogriposis Convulsiones	47/50 (94%) 32/50 (64%) 11/53 (21%) 10/53 (19%)	7/9 (78%) 3/9 (33%) 0/7 0/7
Dobyns and the Brazilian Zika group, 2016		

SINDROME CONGENITO DE ZIKA 3

	Group 1 MIC	Group 2 Normal
Cerebro y TAC		
Calcificaciones Anormalidades del cerebelo Pérdida de volumen de la substancia blanca Ventriculomegalia Colapso de los huesos del cráneo (casco óseo)	55/57 (96%) 19/54 (35%) 55/57 (100%) 53/57 (93%) 30/57 (53%)	9/9 (100%) 0/9 9/9 (100%) 7/9 (78%) 1/9 (11%)
Cerebro y RMN		
Anormalidades de la corteza (PMG) Heterotopia - periventricular Cuerpo calloso anormal Hipoplasia del tallo cerebral	20/20 (100%) 5/18 (28%) 19/20 (95%) 9/20 (45%)	1/1 0/1 1/1 1/1

Dobyns and the Brazilian Zika group, 2016

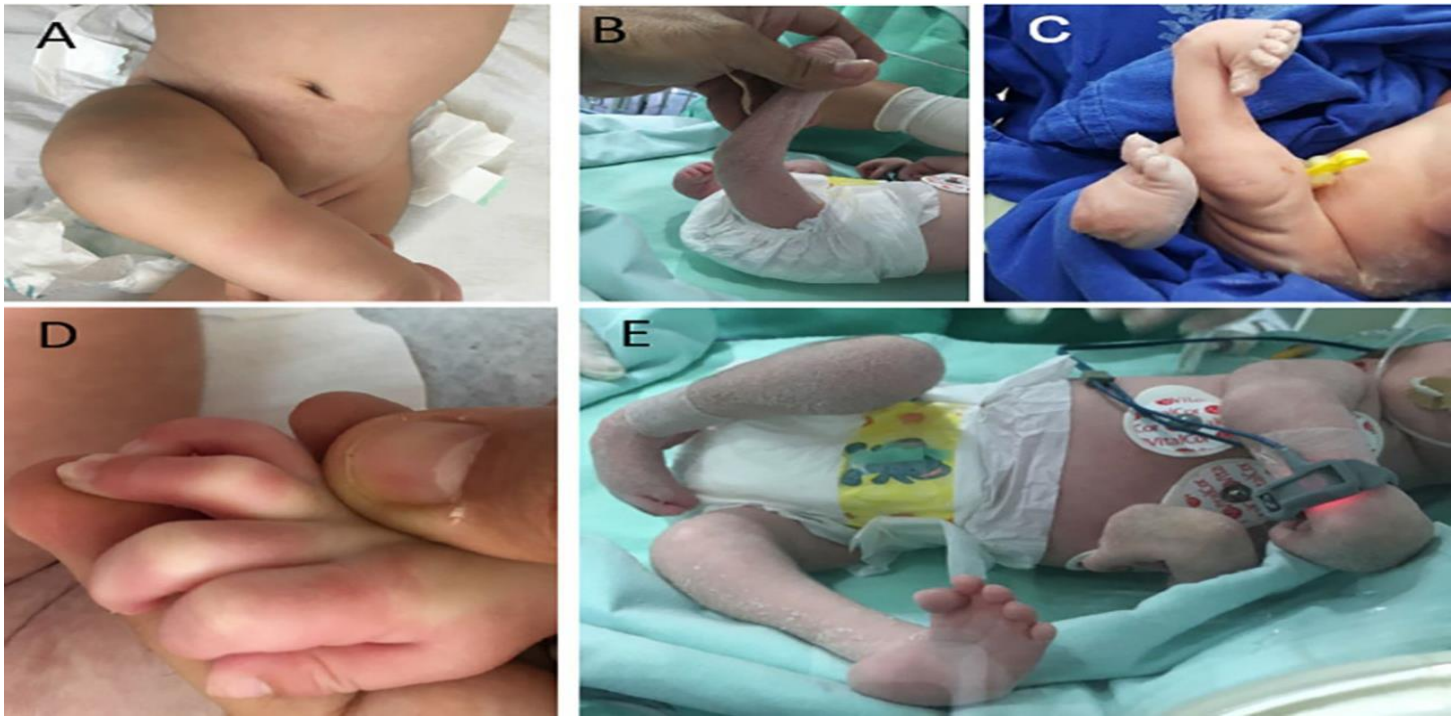
SINDROME CONGENITO DE ZIKA 4

IMAGEN TAC/RMN	Group 1 MIC	Group 2 Normal
Cerebro		
Calcificaciones	55/57 (96%)	9/9 (100%)
Subcorticales o Corticales	51	8
Ganglios de la base	33	2
Substancia blanca periv.	15	3
Tallo cerebral	6	0
Cerebelo	2	0
Brain by MRI		
Abnormal cortex (PMG)	20/20 (100%)	1/1
Heterotopia - periventricular	5/18 (28%)	0/1
Corpus callosum abnormal	19/20 (95%)	1/1
Brainstem hypoplasia	9/20 (45%)	1/1

Dobyns and the Brazilian Zika group, 2016

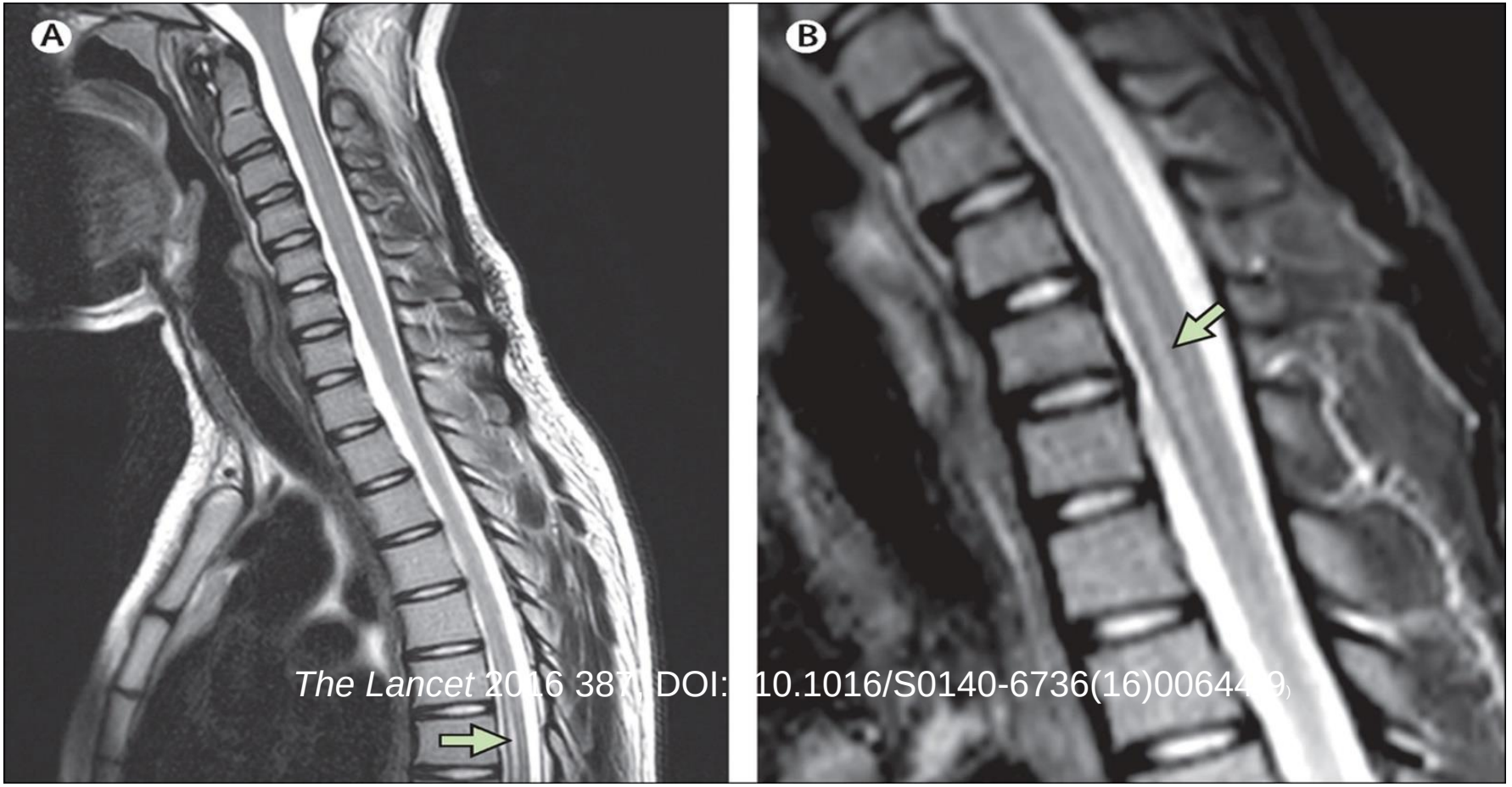
DISTINTAS PRESENTACIONES DE ARTROGRIPOSIS

Fig 1 (A) Contractura en flexion de la rodilla; (B) hiperextension de la rodilla (dislocation); (C) deforme; (D) deformidades en 2nd, 3rd, y 4th dedos; (E) Contracturas articulares en brazos y piernas sin afectar el tronco.



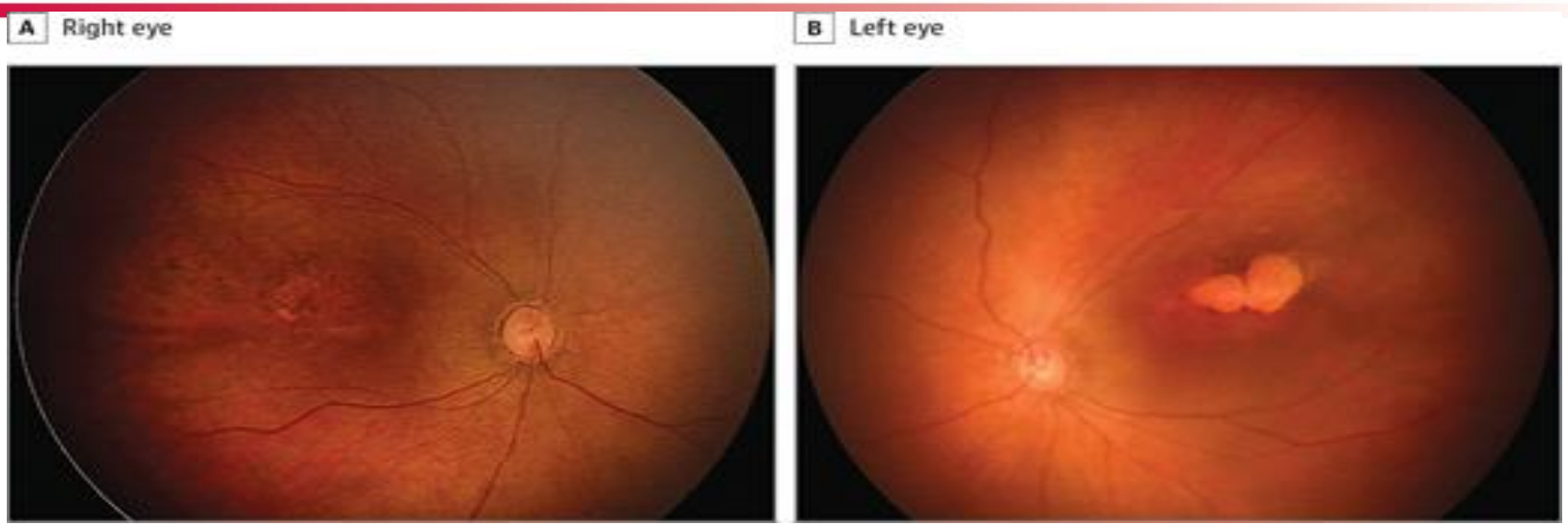
Vanessa van der Linden et al. BMJ 2016;354:bmj.i3899

MIELITIS



The Lancet 2016 387; DOI: 10.1016/S0140-6736(16)00644-9

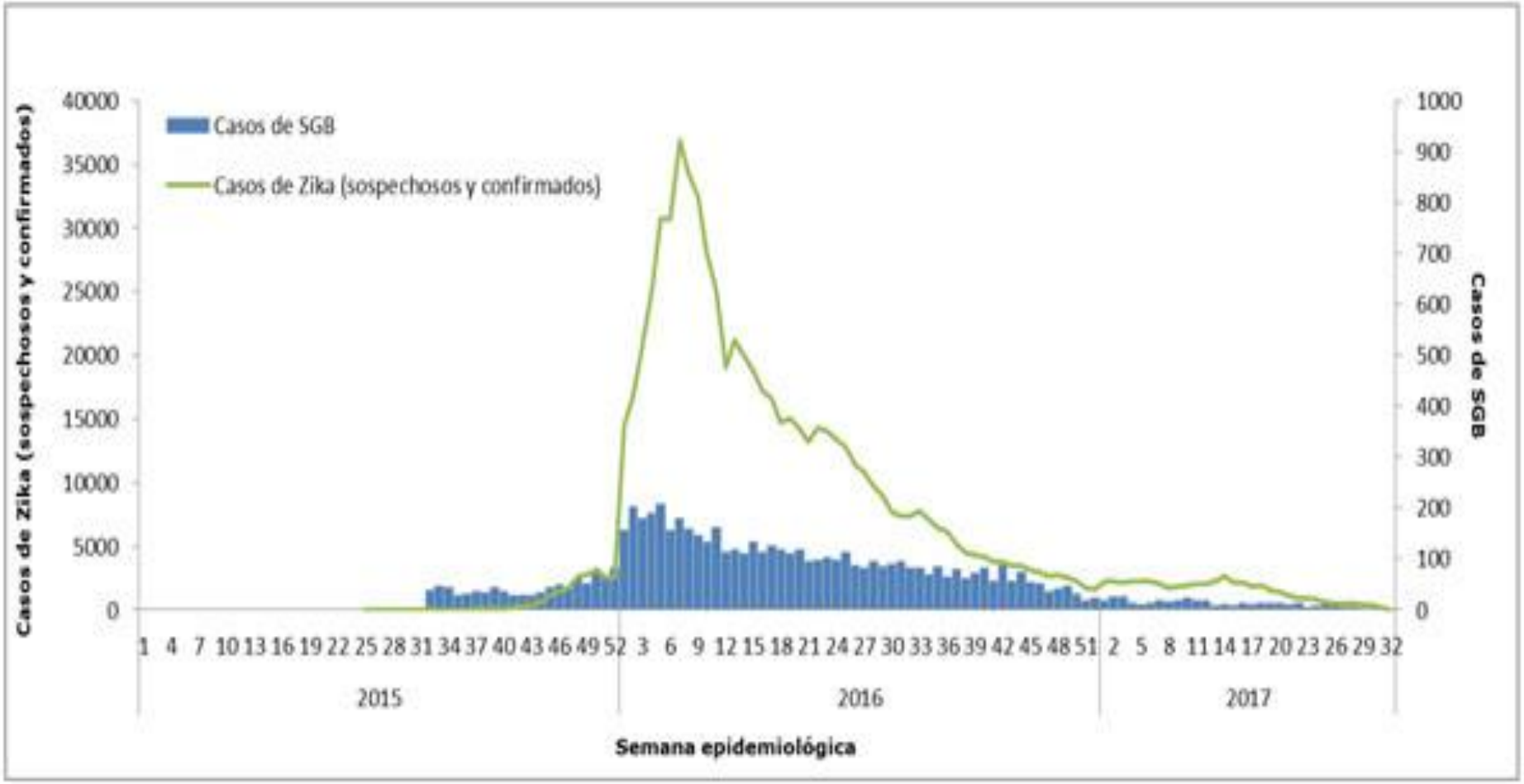
ANOMALIAS OCULARES



El ojo derecho tiene moteado granular y pigmentario en la mácula (A), el ojo izquierdo tiene una lesión atrófica corioretinal lobulada y moteado pigmentario leve (B).

J AMA Ophthalmol. 2016;134(5):529-535. doi:10.1001/jamaophthalmol.2016.0267

SINDROME DE GUILLAIN BARRE

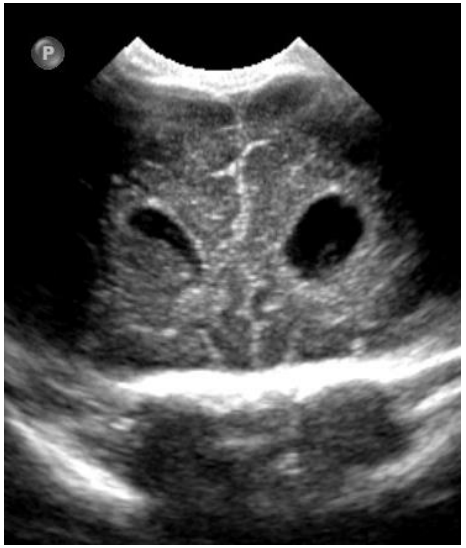


CDC, 2018

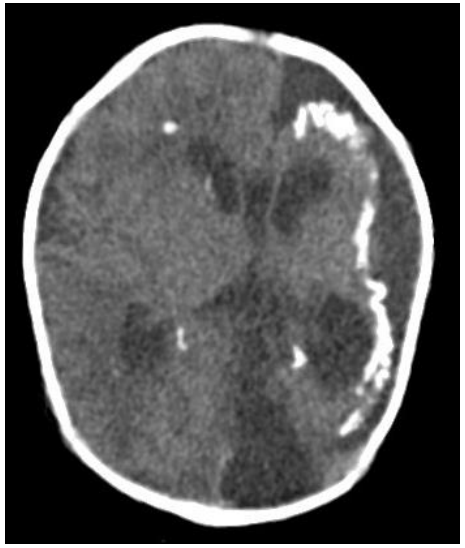
Imagen del cerebro del niño

Caracteristica	Modalidad		
	Ultrasonido	**TAC**	**RMN**
Riesgos	• Mínimo	• Radiación	• Sedación
Ventajas	• Portátil, rápido • Imágenes de línea media • Detecta calcificaciones	• Rápida • Detecta calcificaciones • Identifica las principales malformaciones	• Excelente caracterización de la morfología cortical • Detecta lesiones de la sustancia blanca
Desventajas	• Imágenes poco sensibles de la corteza y la fosa posterior • Necesita una fontanela anterior	• No es portátil • Imágenes poco sensibles de la corteza y la sustancia blanca	• No portatil, relativamente lenta • Imagen poco sensible a las calcificaciones

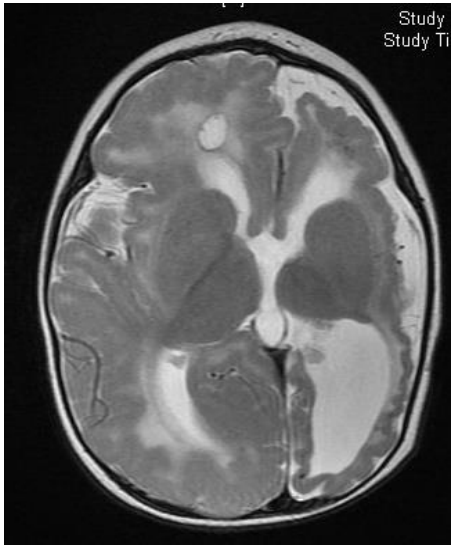
Infección congénita CMV



Ultrasonido



TAC



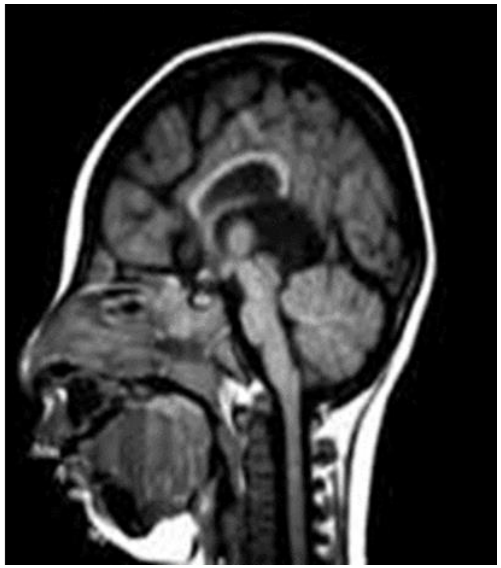
RMN

Jim Bale, Division of Pediatric Neurology Departments of Neurology and Pediatrics University of Utah School of Medicine Salt Lake City, UT

Anormalidades cerebrales Zika Virus

- **Microcefalia**
- **Calcificaciones Intracraniales: subcortical (características) or periventriculares**
- **Displasia cortical: Polimicrogiria, paquijiria, licenzefalia**
- **Hidrocefalia: pasiva u obstructiva**
- **Anormalidades del cuerpo calloso**
- **Infarto cerebral**
- **Disrupción cerebral fetal**

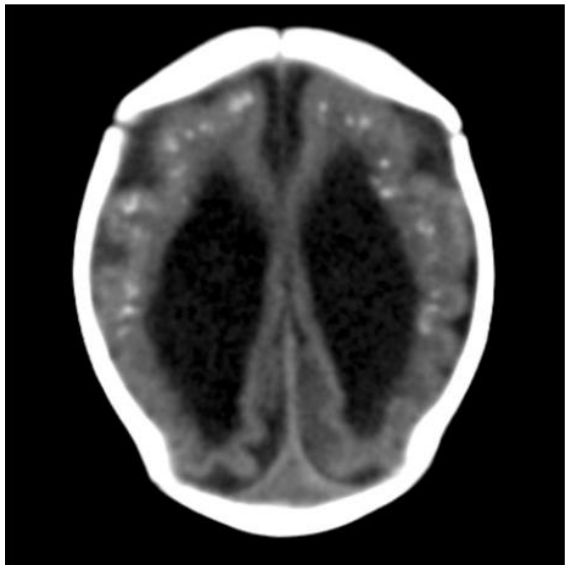
Sindrome Congenito Zika



Source: Google Images: Zika Microcephaly

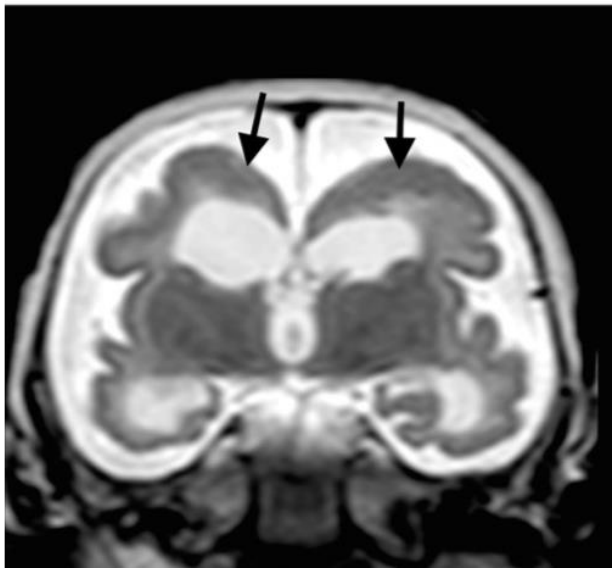
Sindrome Congenito Zika

Calcificaciones



Source: Soares de Oliveira-Szejnfeld, P. Radiology 2016

Displasia Cortical



Source: de Fatima Vasco Aragao M, et al. BMJ 2016

Manejo por imágenes sindrome congénito zika

- **Ultrasonido cranial: immediato en el período neonatal. Considere TAC si la fontanela está cerrada o es muy pequeña.**
- **RMN definitiva cuando esta disponible, la edad del infante y su condición. Recuerde no es bueno para calcificaciones, una característica importante delíndrome congénito de Zika.**
- **Cuando se necesitan imágenes seriadas, escoja la modalidad que le va a dar la mayor información con el menor riesgo.**

Fenómenos de “Desacoplamiento”

- **Algunas convulsiones clínicas no tienen correlación con el electroencefalograma**
- **Convulsiones electrográficas sin correlación clínica**
- **Fenómenos de “Desacoplamiento”**

Consideraciones diagnósticas en relación al momento del inicio de la convulsión

ETIOLOGIA	0-3 DIAS	> 3 DIAS	PREMAT	A TERMINO
HIPOXIA 32%	+		+++	+++
ICH 17% INFARTO 7%	+	+	++	+
↓ GLICEMIA	+		+	+
↓ CA	+	+	+	+
INFEC 14%	+	+	++	++
DM/Genéticas	+	+	++	++
A.DROGAS	+	+	+	+

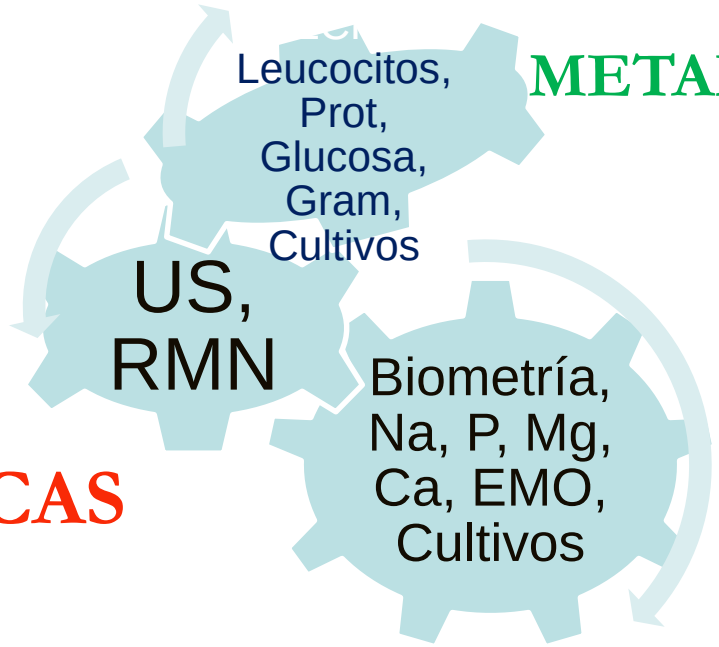
Joseph Volpe, Neurologia Neonatal, 6th edition

CUIDADOS INTENSIVOS

Terapia Intensiva Neonatal, Boston Children's Hospital, (Alcy Torres)

INVESTIGACIONES DE DIAGNOSTICO

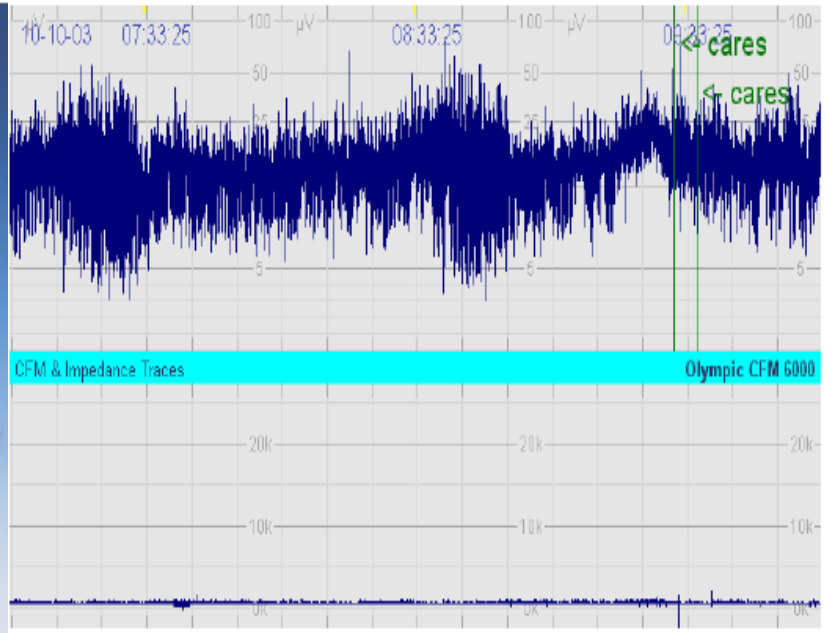
EEG,
LTM,
aEEG



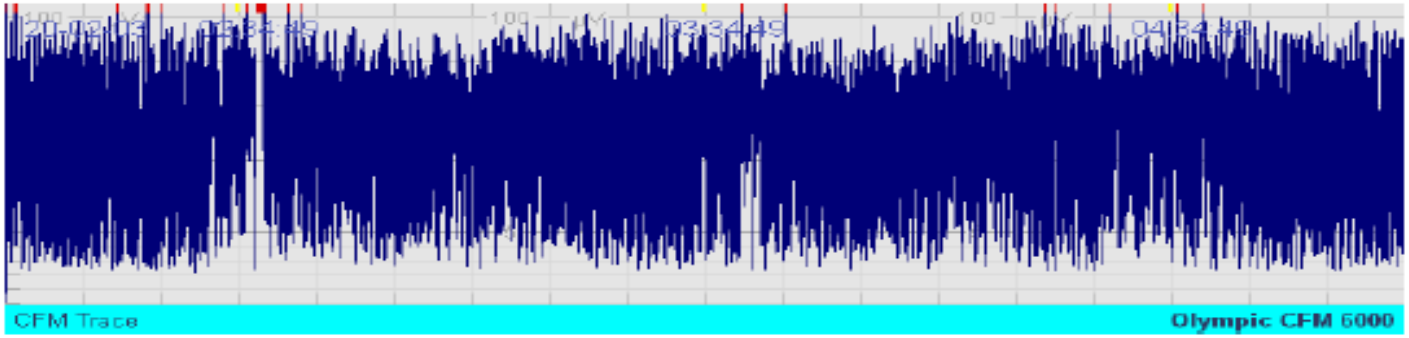
METABOLICAS

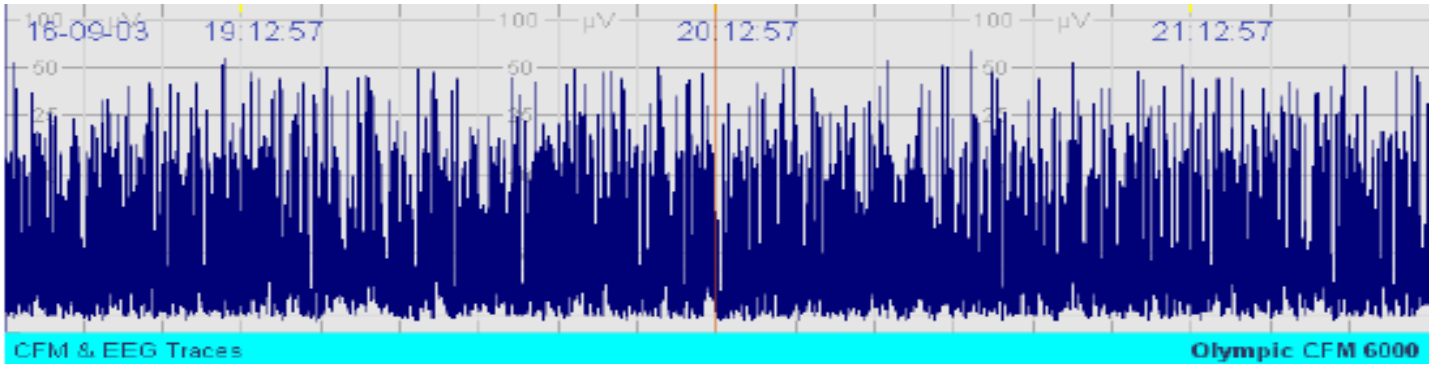
GENETICAS

ELECTROENCEFALOGRAMA DE AMPLITUD aEEG

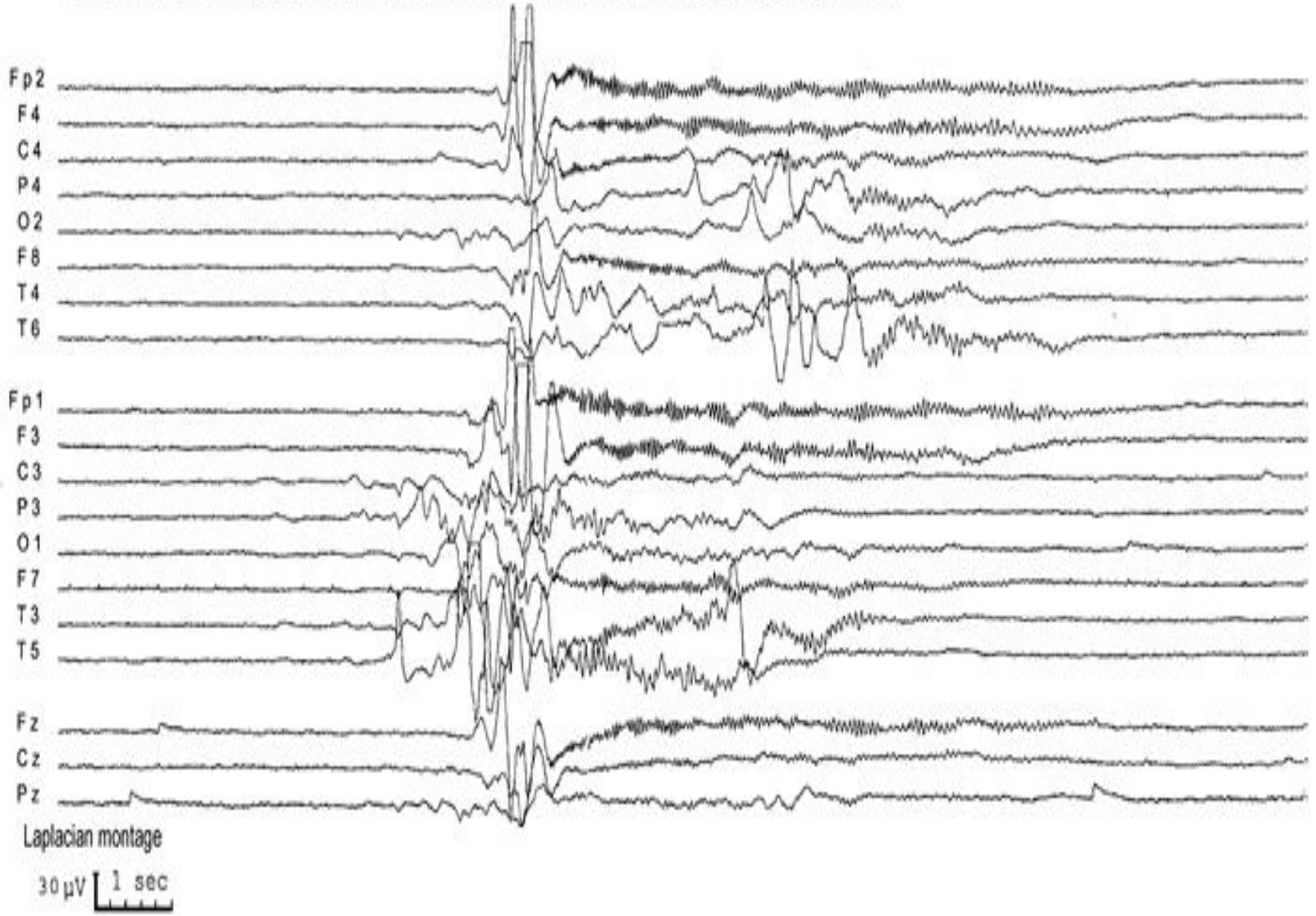


ELECTROENCEFALOGRAMA DE AMPLITUD aEEG





Burst-suppression pattern in a 4 days old neonate with severe hypoxic encephalopathy



TRATAMIENTO DEL ESTADO EPILEPTICO NEONATAL

Estado Epiléptico Precoz vs Establecido

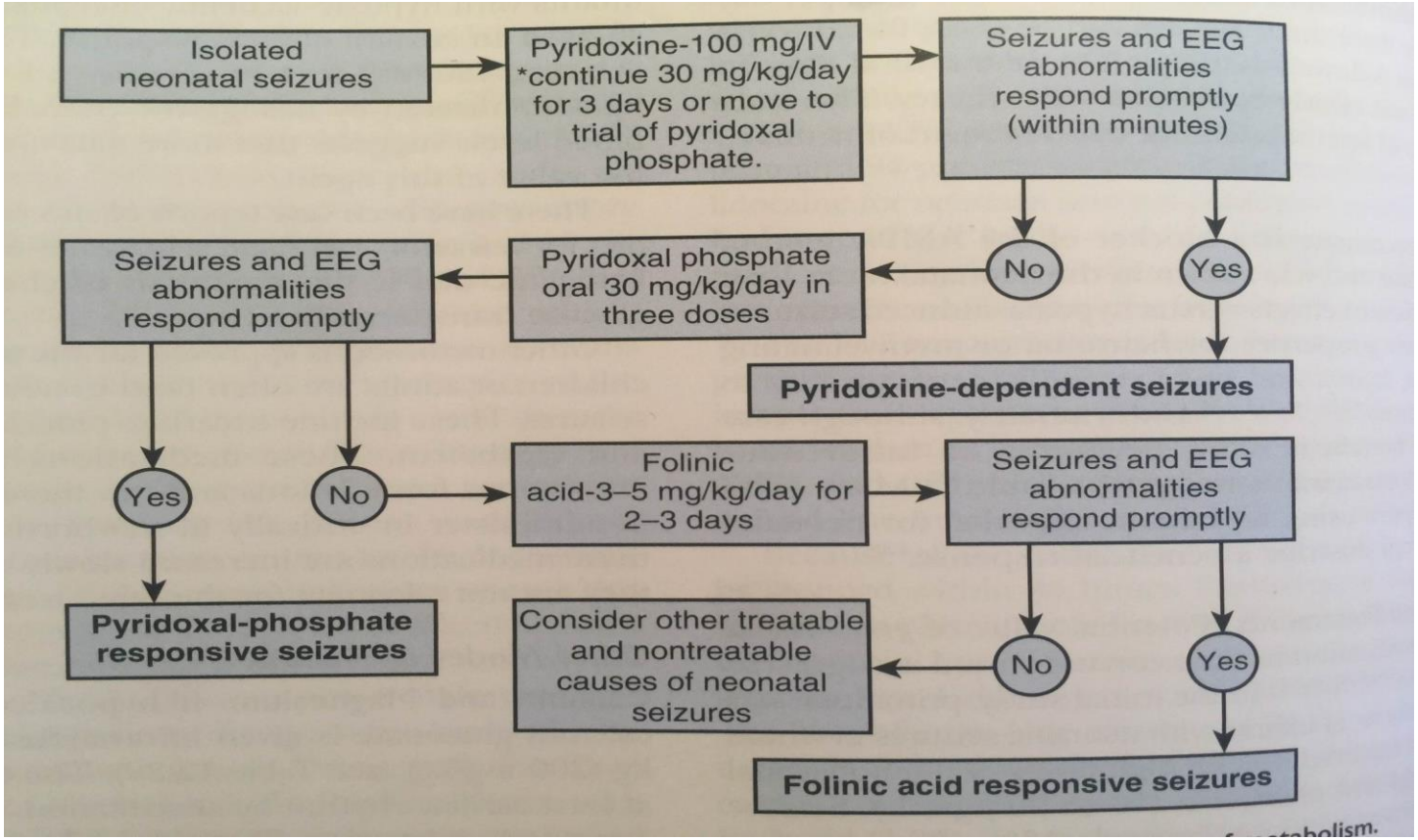
Levetiracetam (Keppra) 40-60mg/Kg/IV
Consider Piridoxina 100 mg IV (Tx. Metabólico)

Tercer AED: Lorazepam 0.1 mg/kg IV(1-4min) Midazolam 0.15mg/Kg/IV
Alternativas: Acido Valproico/Lidocaína/Topiramato

Terapia de Mantenimiento

- 12 horas después de la dosis de carga
- Incluye inicialmente todas las drogas usadas
- Glucosa 8 mg/Kg/min. IV
- Fenobarbital 3-4 mg/Kg/24hr IV, IM, PO (1-2dosis)
- Levetiracetam 40mg/kg/d IV, PO (3 dosis)
- Fosfenitoína 3-4mg/Kg/24hr IV (2 dosis)
- Gluconato de Calcio 500mg/Kg/24hr PO
- Sulfato de Magnesio 50% 0.2ml/Kg/24hr IM

TRATAMIENTOS METABOLICOS



Andrade E, Shaikh Z, Chavez W, Torres A.Medicina (B Aires). 2018;78 Suppl 2:30-35.

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Respuesta al Tratamiento

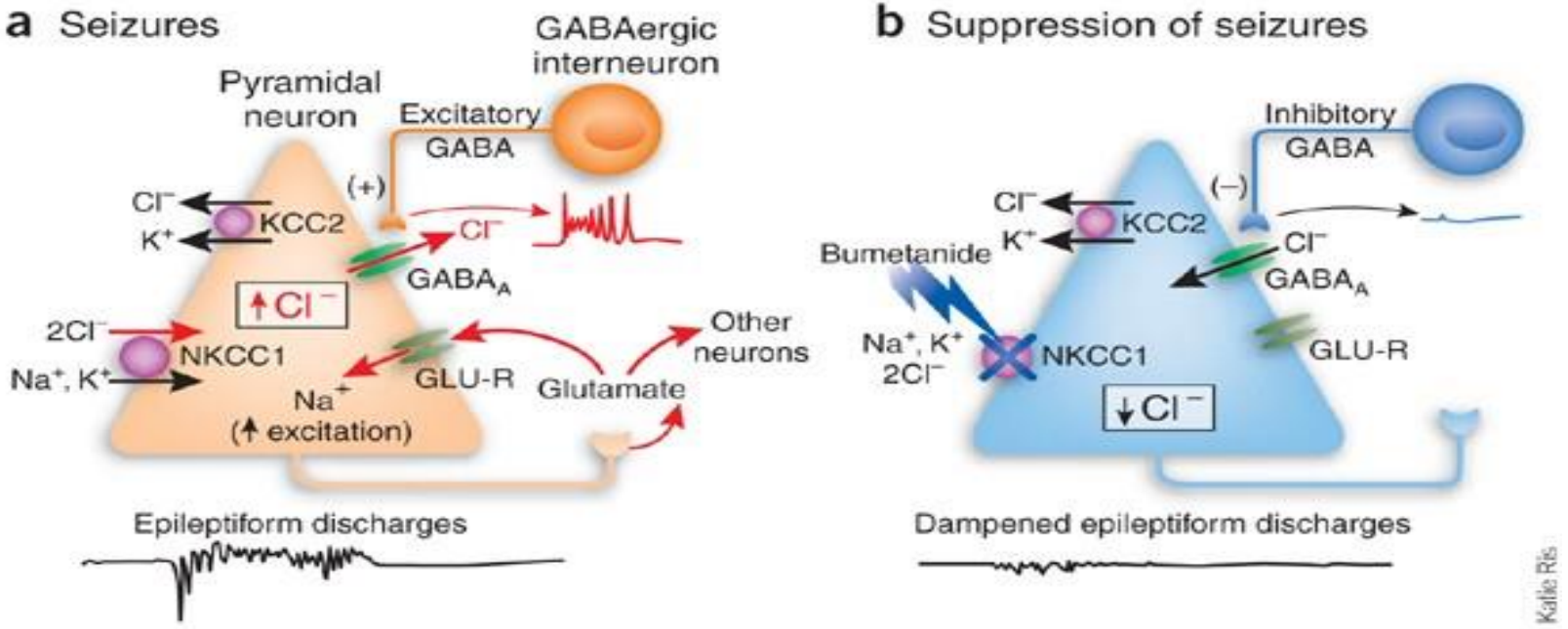
Droga Anticonvulsante	Supresión de las convulsiones
Dosis de carga	Cumulativo %
Fenobarbital 20-40mg/Kg	40%-70%
Levetiracetam 20mg/Kg	?
Fenitoína 20mg/Kg	85%
Lorazepam 0.05-0.10mg/Kg	95-100%

OTRAS DROGAS Y MODALIDADES

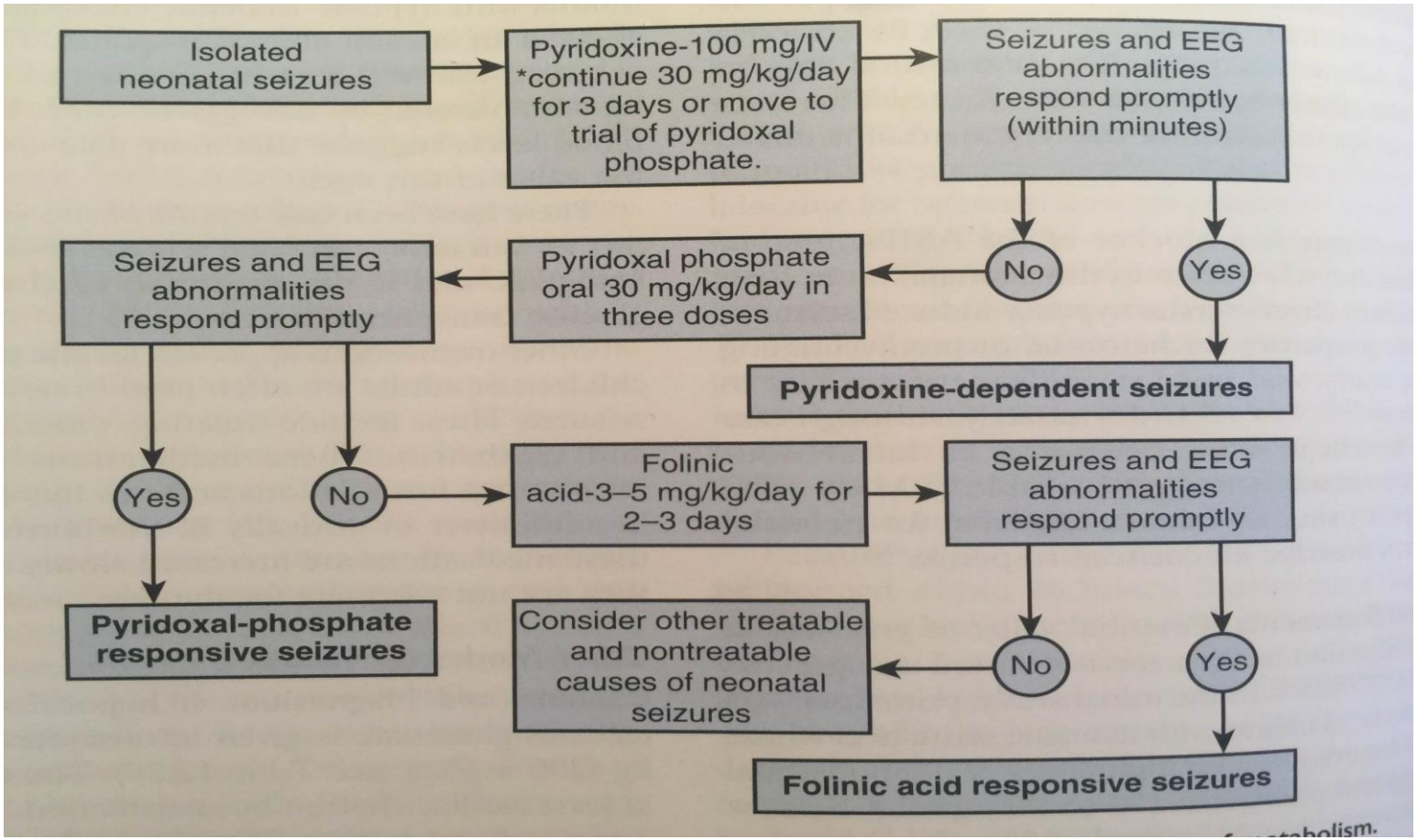
- Altas dosis de Fenobarbital, Levetiracetam
- Midazolam, Lidocaína
- Pentotal, Tiopental
- Bumetanida
- Primidona
- Paraldeído, Clormetiazol
- Dexametasona
- Carbamazepina, Valproato, Lamotrigina Oxcarbazepina, Topiramato, Fenitoína
- Vigabatrina
- Zonizamida

UNA PALABRA SOBRE BUMETANIDA

- **Diurético, inhibe NKCC1, cotransportador de Cl, aumentando cloro celular → Despolarización**
- **Convulsiones que usan GABA (Barbitúricos y**



TRATAMIENTOS METABOLICOS



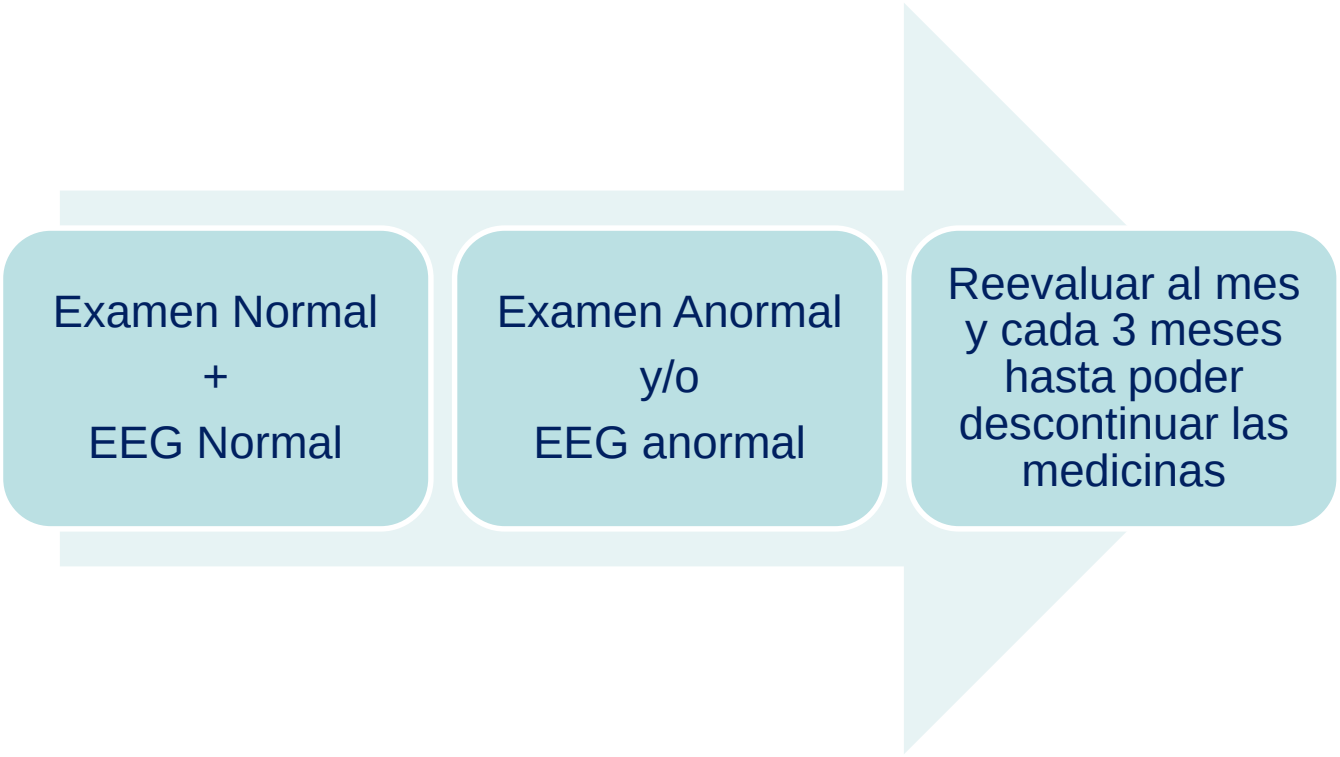
Duración del Tratamiento

Cuál es el riesgo de desarrollar epilepsia?

10-30%

- **Causa de las convulsiones**
- **Examen Neurológico**
- **EEG**

Duración del Tratamiento AED



CASOS ESPECIALES

- **Vigabatrina en malformaciones o complejo de esclerosis tuberosa**
- **Fenobarbital en hipoxia**
- **Carbamazepina en mutaciones KCNQ2**
- **Topiramato o la dieta cetogénica en casos refractarios.**
- **Dieta cetogénica: Alteración del Transporte de Glucosa (Síndrome de Devivo)**

PRONOSTICO

- **Mortalidad 20% – 40%**
- **Sequela Neurológica 25 - 35%**
- **Más grave en los prematuros muy pequeños.**

EEG interictal

- **Anormal de grado severo 90%**
- **Anormal de grado moderado 15 - 30%**

Pronóstico de Convulsiones Neonatales/Madurez

MADUREZ	NORMAL	MUERTOS	SEQUELA
A Término >2500 gm	60%	19%	21%
Prematuros <2500 gm	35%	37%	28%
Prematuros <1500 gm	19%	58%	23%

Pronóstico en relación a la enfermedad neurológica

Enfermedad Neurológica	Desarrollo Normal
HIE	50%
IVH	10%
Hem. subarachnoidea	90%
Hipocalcemia	
Inicio Precoz	50%
Inicio Tardío	100%
Hipoglicemia	50%
Meningitis Bacteriana	50%
Defectos del desarrollo	0%

COMPLICACIONES NEUROLOGICAS DE ZIKA EN ADULTOS

- **40 pacientes 15 mujeres y 25 hombres; 44 años (22-72)**
- **29 (73%) GBS (90% Brighton nivel 1 certeza)**
- **7 (18%) Encefalitis**
- **3 (8%) Mielitis transversa**
- **1 (3%) CIDP**
- **35 pacientes (88%) tuvo evidencia molecular y/o serológica de infección reciente de ZIKV en sangre y/o LCR**
- **De los pacientes positivos para Encefalitis: 3 enfermedad aguda concomitante neuromuscular, 2 Mielitis transversa, y 1 CIDP**

JAMA · August 28, 2017

MONITOREO DURANTE EL PRIMER AÑO

Antes del Alta
Audición/Oftalmología y Tamizaje neonatal

2 weeks

1 month

2 months

3 months

4-6 months

9 months

12 months

- **Crecimiento PC**
- **Crecimiento/nutrición**
- **Alimentación/Tragar**
- **Ex. Neurológico: tono muscular**
- **Contracturas**
- **Ortopeda/Fisiátra/Equipo de PC**
- **A/O/ORL/Gastro**
- **Intervención Temprana: PT, OT, ST**

AAP and Torres, A, Convulsiones Neonatales, 2018

MONITOREO DESDE LA INFANCIA-ADULTOS

- **Manejo del retraso del desarrollo vs discapacidad intelectual**
- **Espasticidad: Lateralización temprana, medicamentos, Botox, bomba de baclofen, aparatos ortopédicos**
- **Convulsiones**
- **Hidrocefalia, shunts, corea en la adolescencia**
- **Cuidado oftalmológico: Retinopatía, Estrabismo**
- **Respiración, sueño, apnea, salibeo**
- **Tubos alimentarios, (constipación)**
- **Incontinencia**
- **Transiciones desde ITP, a pre-escolar, escuela y la vida adulta**
- **Ayuda educacional**

MUCHAS GRACIAS!