FETAL BRAIN DISRUPTION SEQUENCE

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15. celostátní konference fetální mediciny 9.1.2015, Nemocnice na Homolce, Praha

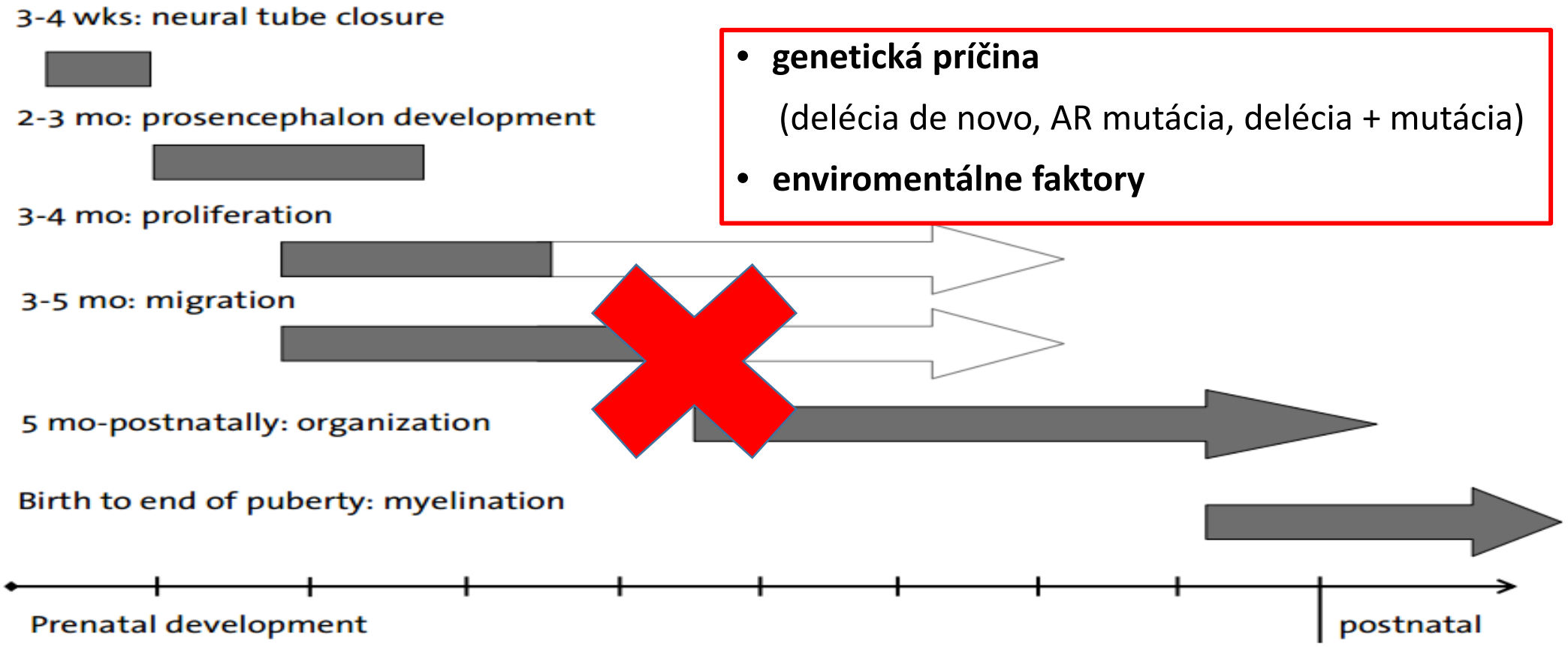
FETAL BRAIN DISRUPTION SEQUENCE - FBDS

- FBDS fenotypový prejav vyplývajúci z narušenia vývoja mozgu v 2. až včasnom 3. trimestri, s mikrohydranencefáliou , poklesom intrakraniálneho tlaku a kolapsom lebečného krytu - Russel et al. 1984

  - závažná kongenitálna mikrocefália
  - zrastené, prípadne prekrývajúce sa lebečné sutúry
  - prominujúca okcipitálna kosť
  - scalp rugae s normálnou vlasou líniou
  - spasticita
  - epi záchvaty / myoklonické kŕče

Russell LJ, Weaver DD, Bull MJ, Weinbaum M (1984). In utero brain destruction resulting in collapse of the fetal skull, microcephaly, scalp rugae, and neurologic impairment: the fetal brain disruption sequence.Am J Med Genet 17:509–521

FETAL BRAIN DISRUPTION SEQUENCE - FBDS



- **genetická príčina**

  (delécia de novo, AR mutácia, delécia + mutácia)
- **enviromentálne faktory**

Figure 6: timeline of human cortical development, peak times. X-axis represents months of gestation.

de Wit, MC., Malformations of the Human Cerebral Cortex Patterns and Causes , 2010, p. 18, ISBN 978-90-5335-305-9

FETAL BRAIN DISRUPTION SEQUENCE - Etiopatogenéza

Exogénny inzult ?

- obliterácia arteria carotis interna bilaterálne
- difúzny hypoxicko-ischemický inzult
  - TTTS / TRAP sekvencia
  - infekčné agens s nekrotizujúcou vaskulitídou (TORCH)
  - expozícia teratogénom / drogám (kokaín)
  - trauma (tentamen suicidii, autonehoda)

Genetická príčina ?

- Konsanguinita – Anatólia (Turecko)
- Izolovaný výskyt mikrocefálie
  - v.s. AR viazanosť
- v literatúre sa prelína terminológia:
  - FBDS
  - microhydranecephalia
  - hereditary brain degeneration
  - microcephaly with simplified gyral pattern
  - microlissencephaly

FBDS fenotyp a familiárny výskyt

- Fetal brain disruption sequence in sisters. Alexander IE al.(1995). Europ J Pediat 154:654–657.

- The novel genetic disorder microhydranencephaly maps to chromosome 16p13.3-12.1.

  Kavaslar GN. Et al. (2000). Am J Hum Genet 66:1705–1709

- Hereditary fetal brain degeneration resembling fetal brain disruption sequence in two sibships. Schram A . et al. (2004). Am J Med Genet 127A:172–182.

- Familial microhydranencephaly, a family that does not map to 16p13.13-p12.2: relationship with hereditary fetal brain degeneration and fetal brain disruption sequence. Behunova J. et al. (2010) Clin Dysmorphol. 19(3):107-18

konsanguinita = MHAC - 16p13.3-p12.2

FBDS fenotyp a familiárny výskyt

- Human mutations in NDE1 cause extreme microcephaly with lissencephaly [corrected]. Alkuraya FS et al. Am J Hum Genet. 2011 May 13;88(5):536-47
- Novel NDE1 homozygous mutation resulting in microhydranencephaly and not microlyssencephaly. Guven A et al. Neurogenetics. 2012 Aug;13(3):189-94
- Deletion 16p13.11 uncovers NDE1 mutations on the non-deleted homolog and extends the spectrum of severe microcephaly to include fetal brain disruption. Paciorkowski AR et al. Am J Med Genet A. 2013 Jul;161A(7):1523-30.
- The scaffold protein Nde1 safeguards the brain genome during S phase of early neural progenitor differentiation. Elife. 2014 Sep 23;3:e03297. Houlihan SL et al.

NDE1 homozygotná mutácia 16p13.11 = mikrohydranencefália → FBDS

Kazuistika – fenotypu fetal brain disruption sequence

- 28 ročná primigravida RA a OA negat
- laboratórny skríning v gravidite v norme
- prenatálny biochemický skríning v norme
- UZ skríning I. trimestra v rajóne v norme
- v 20 t. g. hospitalizácia pre zakrvácanie
  realizovaný aj UZ skríning II.trimestra
  (morfol. v norme, BPD – 20+6, HC 20+3)

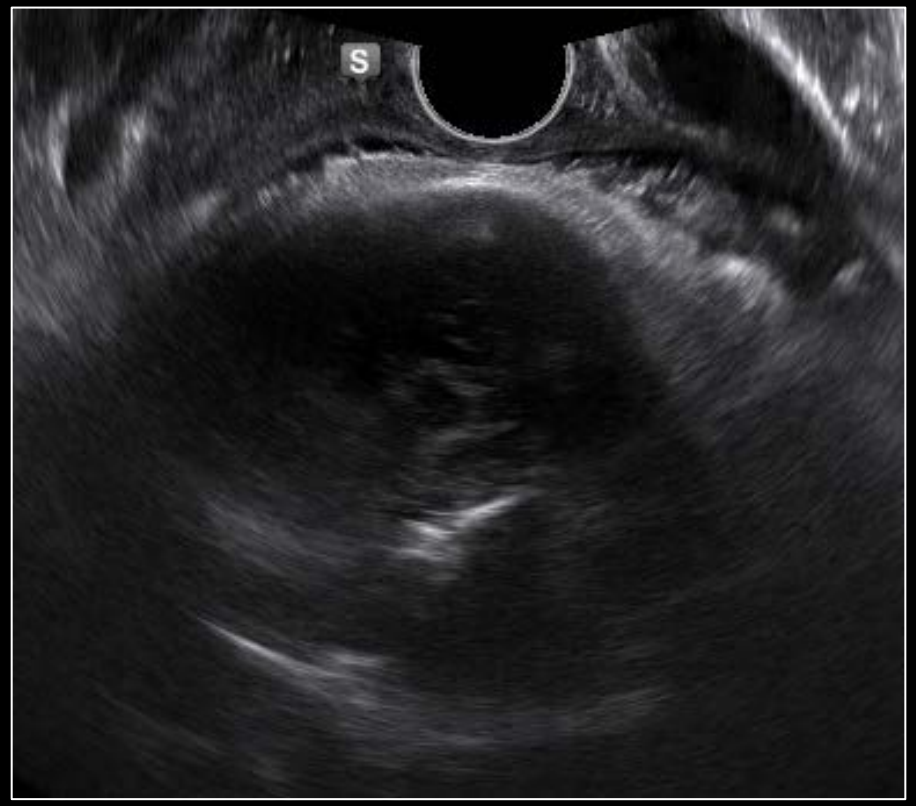
- UZ skríning III. trimestra v 29 t.g. v rajóne
  BPD 27+4, HC 26+4
  AC 28+5, FL 29+0

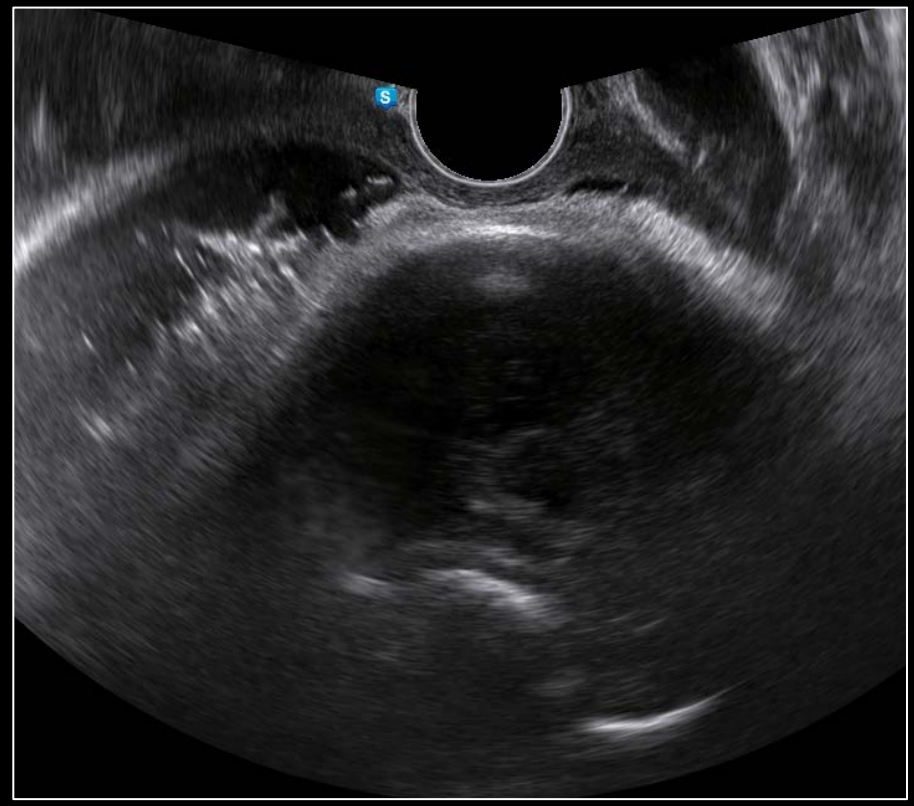
  FL/BPD 80 % (71-87%) FL/AC 22% (20-24%)
  HC/AC 1,00 (1,01-1,21) FL/HC 22 % (19-21%)
  BPD/OFD 81% (70-86%)

- 37 t.g. prenatálna poradna na klin. pracovisku
  susp. porucha vývoja neurokránia, mikrocefália

Kazuistika – fenotypu fetal brain disruption sequence

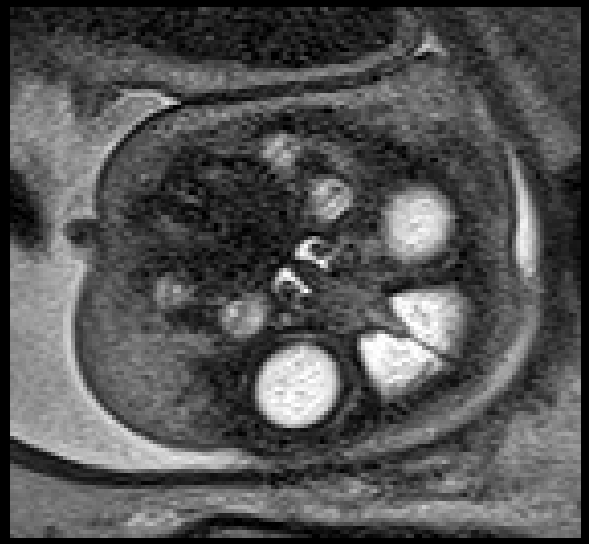
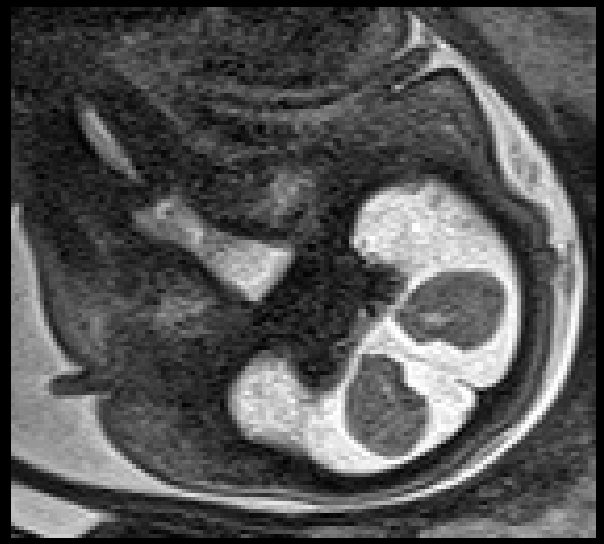
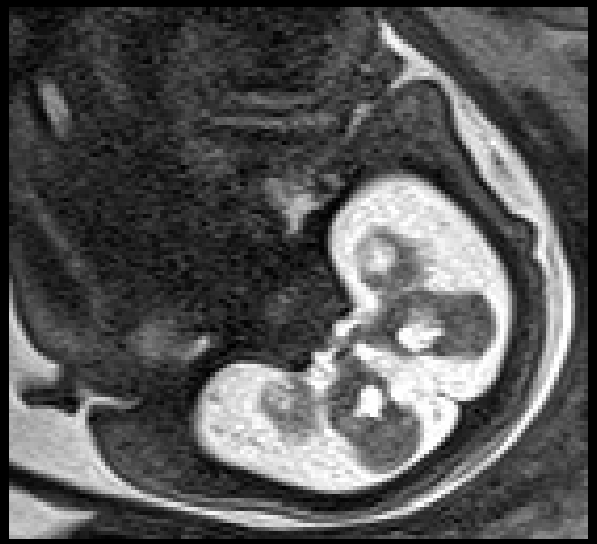
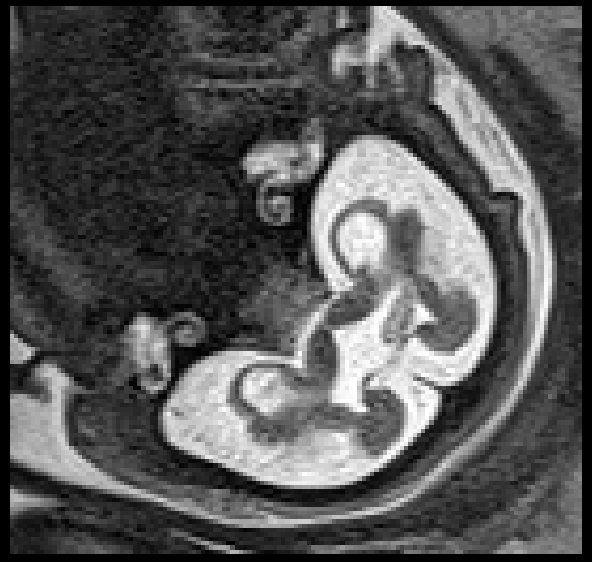
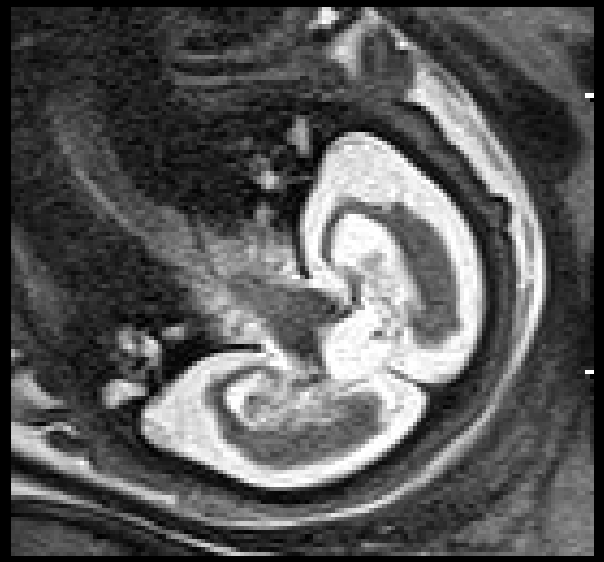
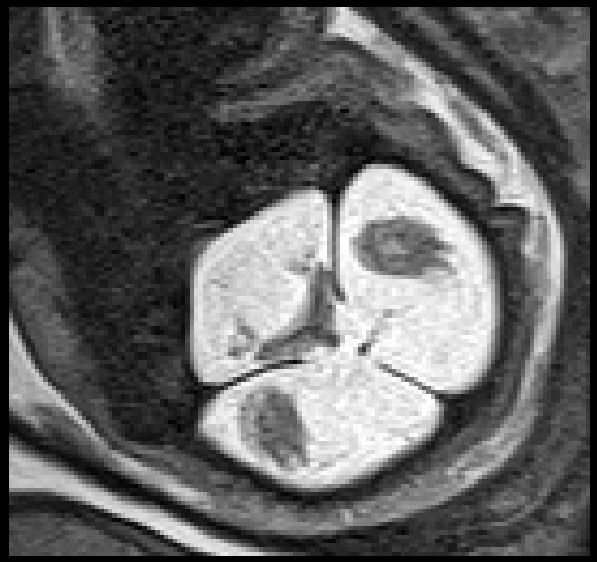
- limitované akustické podmienky , susp. abnormálny vývoj neurokránia plodu
- HC sa nedá nastaviť, BPD 75 mm - 30+0 (-6 SD)
- AC 330,51 mm - 36+6, FL 70,62 mm - 36+1





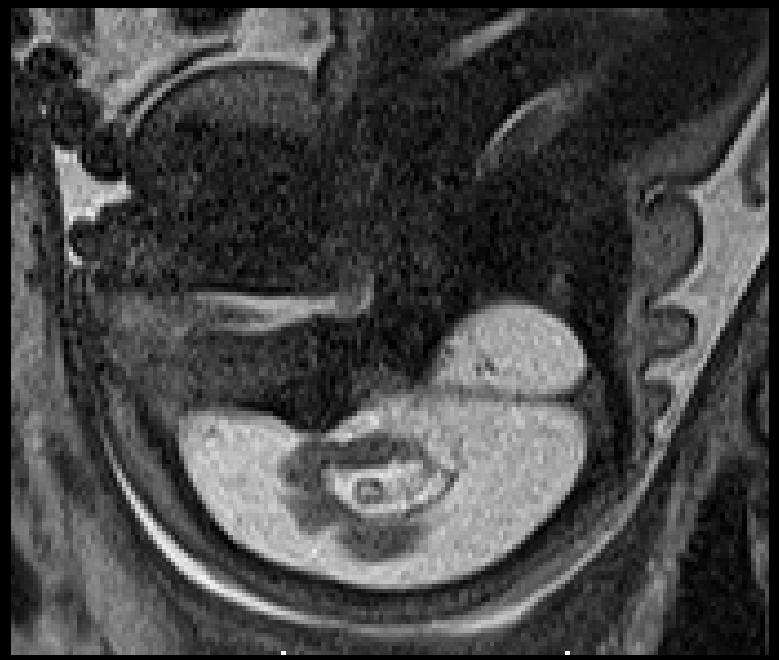
Transvaginálna sonografia neurokránia plodu v 37. týždni gestácie

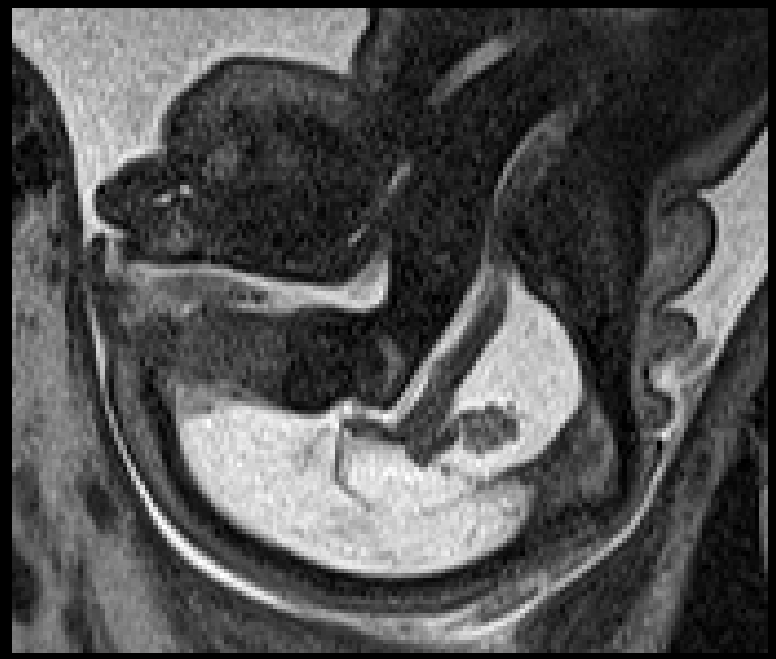
Kazuistika – fenotypu fetal brain disruption sequence

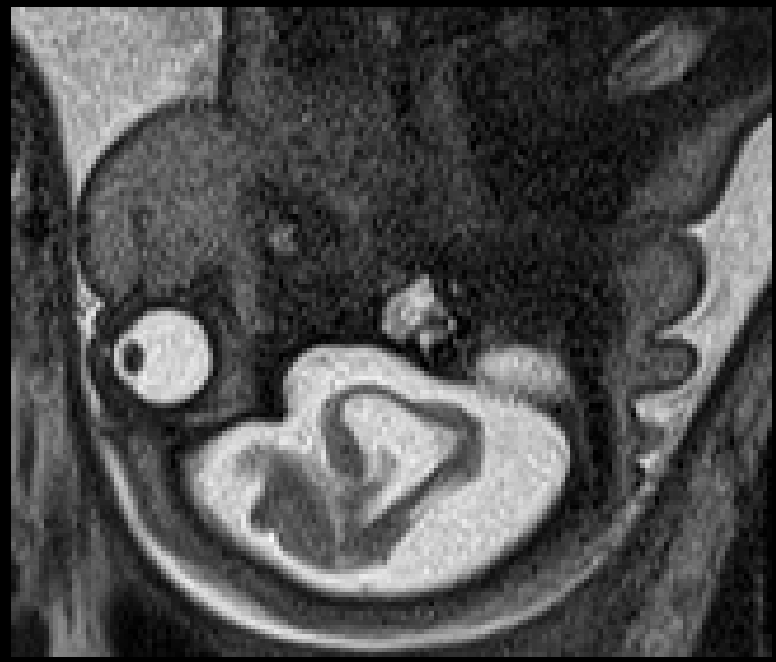







MRI T2 sekvencie , 38. gestačný týždeň

Kazuistika – fenotypu fetal brain disruption sequence







MRI T2 sekvencie , 38. gestačný týždeň

Kazuistika – fenotypu fetal brain disruption sequence

- pôrod v 39 t.g. cisársky rezom
- dievča, 3010 g / 48 cm , APG 9/10/10, ph 7,32
- OFC 28 cm (-4SD)

- po 36 hod. preklad na odd. patol. novorodencov
  - dodiagnostikovanie, konziliárne vyšetrenia (neurológ, oftalmológ, genetik)

- USG CNS : nemožné – uzavretie fontanel

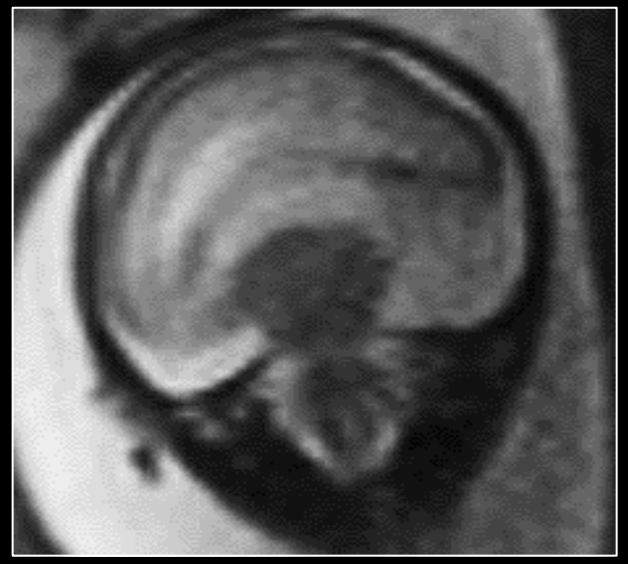
- Neurol: hypertonus a generalizované myoklónie

- Oftalmol: bez ložiskových zmien očného pozadia
- skríning katarakty negatívny

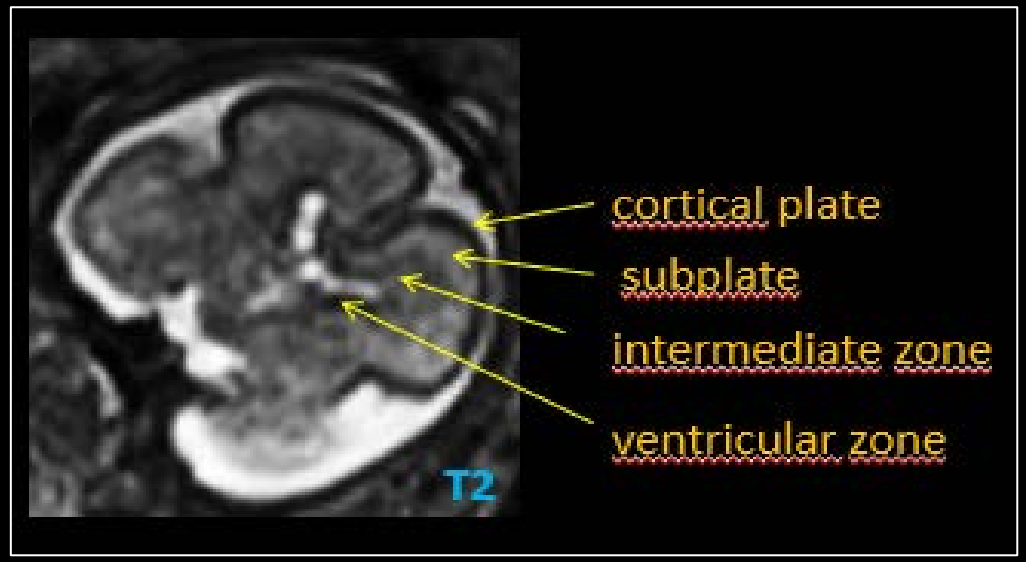
- Genetika: 46, XX
  a CGH - prebieha

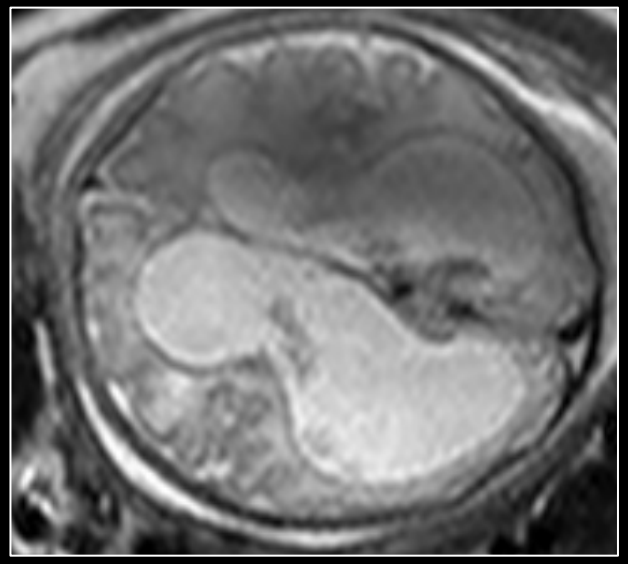
- zvyšovaný enterálny príjem toleruje, ale sondované
- v hlbokom spánku na chrbte chabá mandibula so zapadávaním jazyka

Diferenciálna diagnostika FBDS

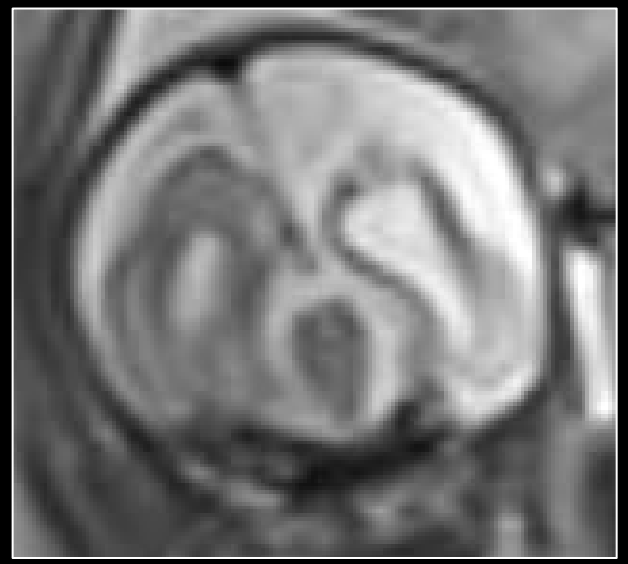


Holoprosencefália

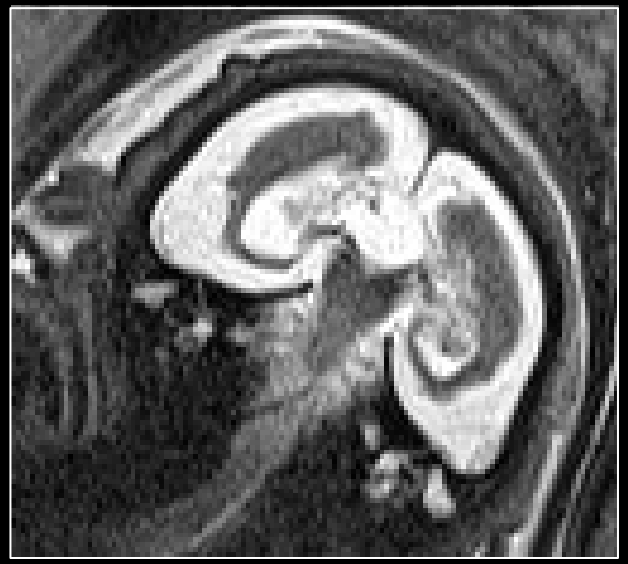




Hydrocefalus



Encefalomalácia a kortikálna atrofia
po prerušení TRAP sekvencie akardia



Fetal brain disruption sequence

Pavone et al. Italian Journal of Pediatrics 2014, 40:79
http://www.ijponline.net/content/40/1/79

ITALIAN JOURNAL OF PEDIATRICS

REVIEW Open Access

Hydranencephaly: cerebral spinal fluid instead of cerebral mantles

Piero Pavone[1*], Andrea D Praticò[1], Giovanna Vitaliti[1], Martino Ruggieri[2], Renata Rizzo[3], Enrico Parano[4], Lorenzo Pavone[1], Giuseppe Pero[5] and Raffaele Falsaperla[1]

Table 1 Differential diagnosis of hydranencephaly with hydrocephalus, holoprosencephaly, porencephaly

	Hydranencephaly	Hydrocephalus	Holoprosencephaly	Porencephaly
Head circumference	Normal or slightly smaller	Larger	Normal	Normal
Midline malformations	Absent	Absent	Present	Absent
Brainstem anomalies	Absent	Absent	Present	Absent
Intact cortical rim	Absent	Present	Present	Present
Dilated third ventricle	Absent	Present only in obstructive forms	Absent	Absent
Angiographic investigation	Bilateral internal carotid artery occlusion (not always)	Normal	Normal	Involvement of middle cerebral artery resulting in localized areas of cortical destruction
Facial malformations	Absent	Absent	Present	Absent
Surgical treatment	Doubt	Useful	Not advisable	Not advisable

Prenatal Sonography in Hydranencephaly

Findings During the Early Stages of Disease

Waldo Sepulveda, MD, Hernan Cortes-Yepes, MD, Amy E. Wong, MD, Victor Dezerega, MD, Edgardo Corral, MD, Gustavo Malinger, MD

http://www.jultrasoundmed.org/content/31/5/799.full.pdf

Table 1. Fetal Hydranencephaly: Clinical Cases

Case	MA, y	Parity	Reason for Referral	GA, wk	HC, mm	TCD, mm	Sonographic Findings	Remarks
1	17	0	Abnormal fetal brain at second-trimester scan	23	212	18[a]	Absent cerebral hemispheres; homogeneous material filling the supratentorial space, normal appearance of the cerebellum and brain stem, portions of the choroid plexuses and the cerebral falx identified	Drug abuse, TOP
2	19	0	Abnormal fetal brain at second-trimester scan	21	173	18[a]	Same as in case 1 plus posterior aspect of the occipital cortex visible	Term delivery, early neonatal death
3	28	2	Threatened miscarriage, suspicion of holoprosencephaly	21	196	21	Same as in case 1 plus remnants of lateral ventricles, circle of Willis present	Miscarriage, postmortem examination confirmed prenatal findings
4	25	2	Suicide attempt	23	218	20[a]	Same as in case 1 plus remnants of lateral ventricles	Abortion attempt at 20 wk, suicide attempt at 23 wk, TOP

GA indicates gestational age; HC; head circumference; MA, maternal age; TCD, transverse cerebellar diameter; and TOP; termination of pregnancy.
[a]Values below the fifth percentile according to gestational age.[7]

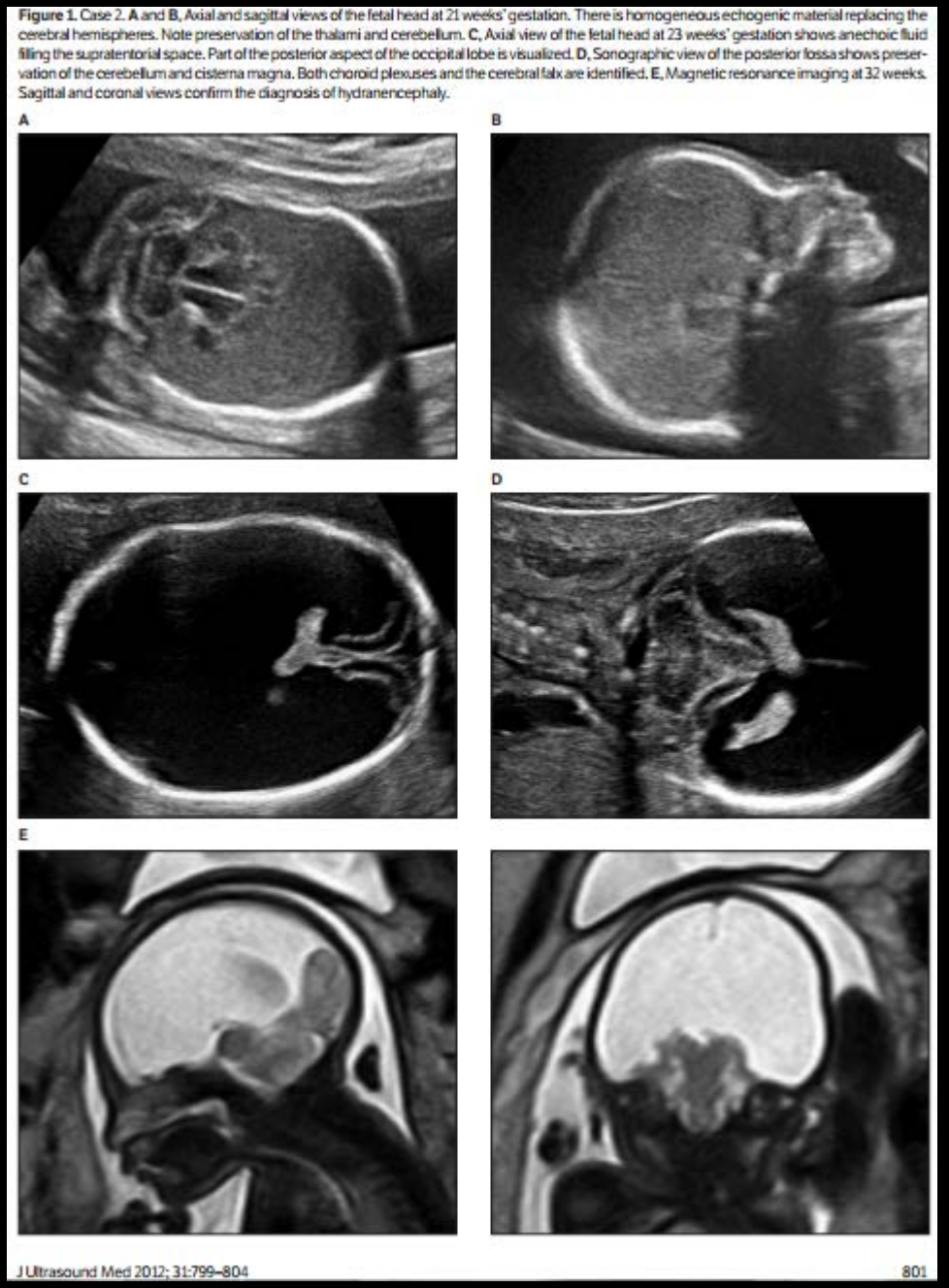
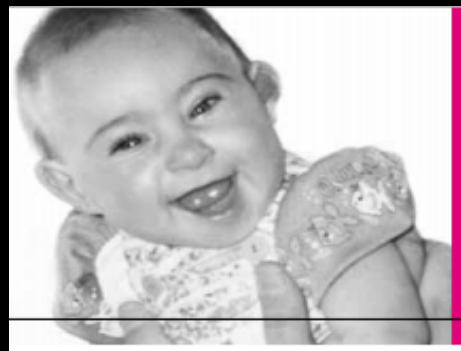


Figure 1. Case 2. **A** and **B**, Axial and sagittal views of the fetal head at 21 weeks' gestation. There is homogeneous echogenic material replacing the cerebral hemispheres. Note preservation of the thalami and cerebellum. **C**, Axial view of the fetal head at 23 weeks' gestation shows anechoic fluid filling the supratentorial space. Part of the posterior aspect of the occipital lobe is visualized. **D**, Sonographic view of the posterior fossa shows preservation of the cerebellum and cisterna magna. Both choroid plexuses and the cerebral falx are identified. **E**, Magnetic resonance imaging at 32 weeks. Sagittal and coronal views confirm the diagnosis of hydranencephaly.



AAN Summary of Evidence-based Guideline for CLINICIANS

PRACTICE PARAMETER: EVALUATION OF THE CHILD WITH MICROCEPHALY (AN EVIDENCE-BASED REVIEW)

This is a summary of the American Academy of Neurology (AAN) and Child Neurology Society guideline (*Neurology*® 2009;73:887–897) regarding evaluation of the child with microcephaly. Recommendations are presented for neuroimaging, genetic testing, and screening for coexistent conditions.

NEUROIMAGING

Neuroimaging may be considered useful in identifying structural causes in the evaluation of the child with microcephaly (**Level C**).

MRI often reveals findings that are more difficult to visualize on CT, such as migrational disorders, callosal malformations, structural abnormalities in the posterior fossa, and disorders of myelination, and is considered the superior diagnostic test.

GENETIC TESTING

Targeted genetic testing may be considered in the evaluation of the child with microcephaly in order to determine a specific etiology (**Level C**).

Microcephaly has been associated with numerous genetic etiologies. Because the genetics of microcephaly is a rapidly evolving field, current data underestimate the importance and relevance of genetic testing as part of the diagnostic evaluation. Many of the microcephaly genes have been associated with specific phenotypes, allowing targeted clinical testing. However, insufficient data showing the diagnostic yield of these tests preclude specific recommendations for use.

METABOLIC TESTING

There is insufficient evidence to support or refute obtaining metabolic testing on a routine basis for the evaluation of the newborn or infant with microcephaly (**Level U**).

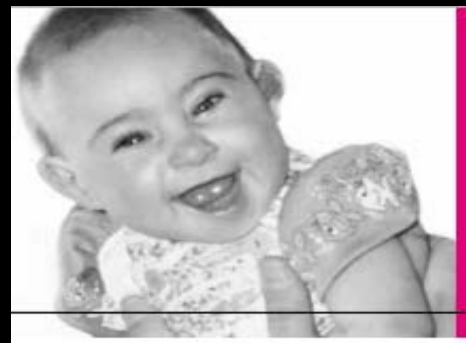
Microcephaly is common in global developmental delay (GDD) and the yield of metabolic testing may be higher when the following are present: parental history of consanguinity, family history of similar symptoms in relatives, episodic symptoms, developmental regression, extracranial organ failure, or specific findings on neuroimaging. Metabolic testing may have a higher yield when microcephaly remains unexplained after other evaluations have been done.

MRI

aCGH, WGS, SNP array

maternal PKE

Mo cofactor def



AAN Summary of Evidence-based Guideline for CLINICIANS

PRACTICE PARAMETER: EVALUATION OF THE CHILD WITH MICROCEPHALY (AN EVIDENCE-BASED REVIEW)

EPILEPSY

Because children with microcephaly are at risk for epilepsy, physicians may consider educating caregivers of children with microcephaly on how to recognize clinical seizures (**Level C**).

There are insufficient data to support or refute obtaining a routine EEG in a child with microcephaly (**Level U**).

CEREBRAL PALSY

Because children with cerebral palsy (CP) are at risk for developing acquired microcephaly, serial HC measurements should be followed (**Level A**).

Because children with microcephaly are at risk for CP, physicians and other care providers may consider monitoring them for early signs so that supportive treatments can be initiated (**Level C**).

MENTAL RETARDATION

Because children with microcephaly are at risk for developmental disability, physicians should periodically assess development and academic achievement to determine whether further testing and rehabilitative efforts are warranted (**Level A**).

OPHTHALMOLOGICAL AND AUDIOLOGICAL DISORDERS

Screening for ophthalmological abnormalities in children with microcephaly may be considered (**Level C**).

Certain microcephaly syndromes are characterized by sensory impairments. Early identification of visual and hearing deficits may help identify a syndrome and the need for supportive care of the child.

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

A developmental and genetic classification for malformations of cortical development: update 2012

A. James Barkovich,[1] Renzo Guerrini,[2,3] Ruben I. Kuzniecky,[4] Graeme D. Jackson[5,6] and William B. Dobyns[7,8]

1. Malformations due to abnormal neuronal and glial proliferation or apoptosis
    - 1.1 Decreased proliferation/increased apoptosis: Microcephaly with/without normal cortex.
    - 1.2 Increased proliferation/decreased apoptosis: Megalencephaly with/without normal cortex.
    - 1.3 Abnormal proliferation (abnormal cell types)
2. Malformations due to abnormal neuronal migration
    - 2.1 Lissencephaly/subcortical band heterotopia spectrum
    - 2.2 Cobblestone complex
    - 2.3 Heterotopia
3. Malformations due to abnormal cortical organization (including late neuronal migration)
    - 3.1 Polymicrogyria and schizencephaly

Ďakujem za pozornosť