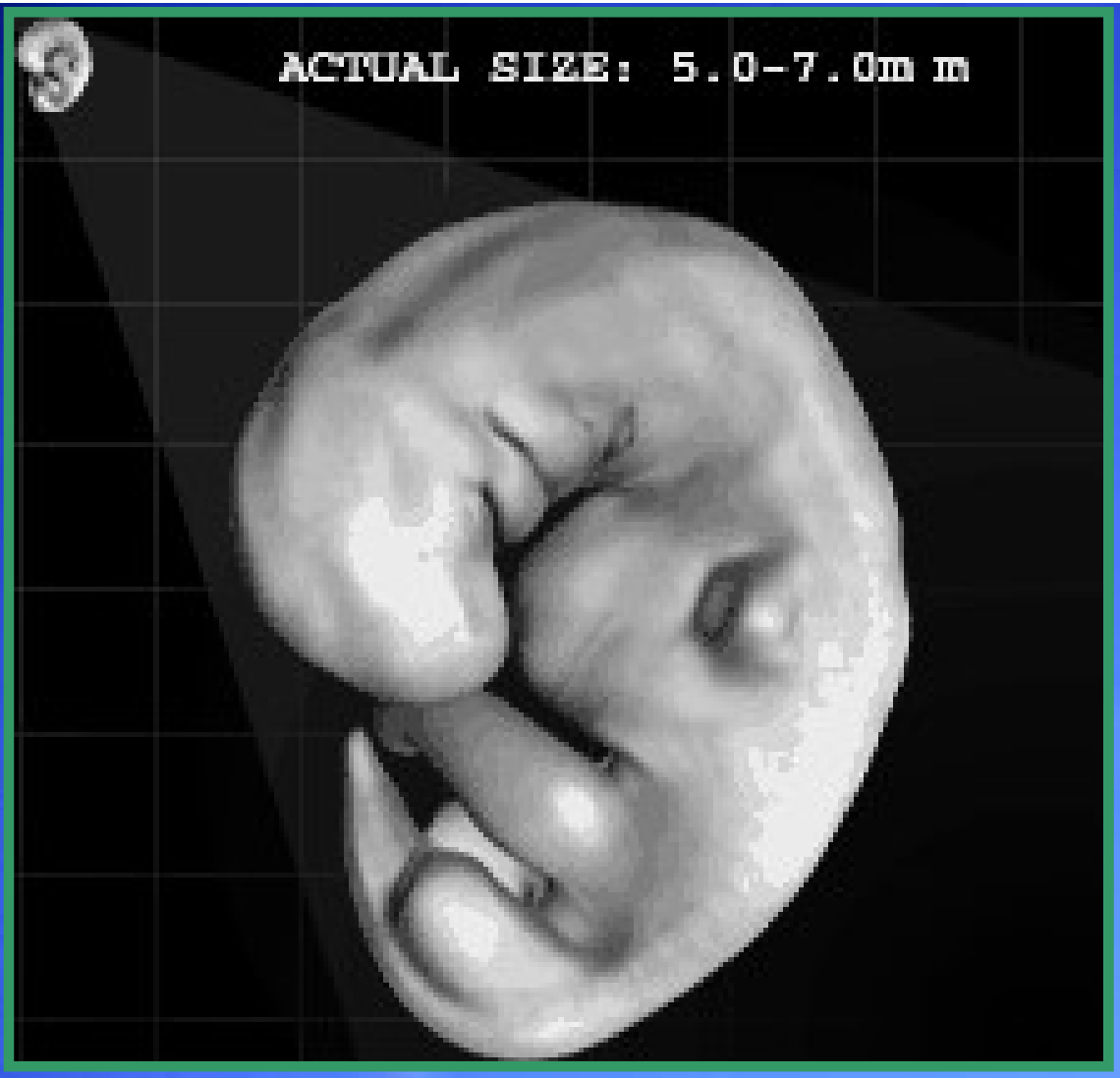
Disturbi induzione ventrale e proliferazione
3°

Tolman 2024

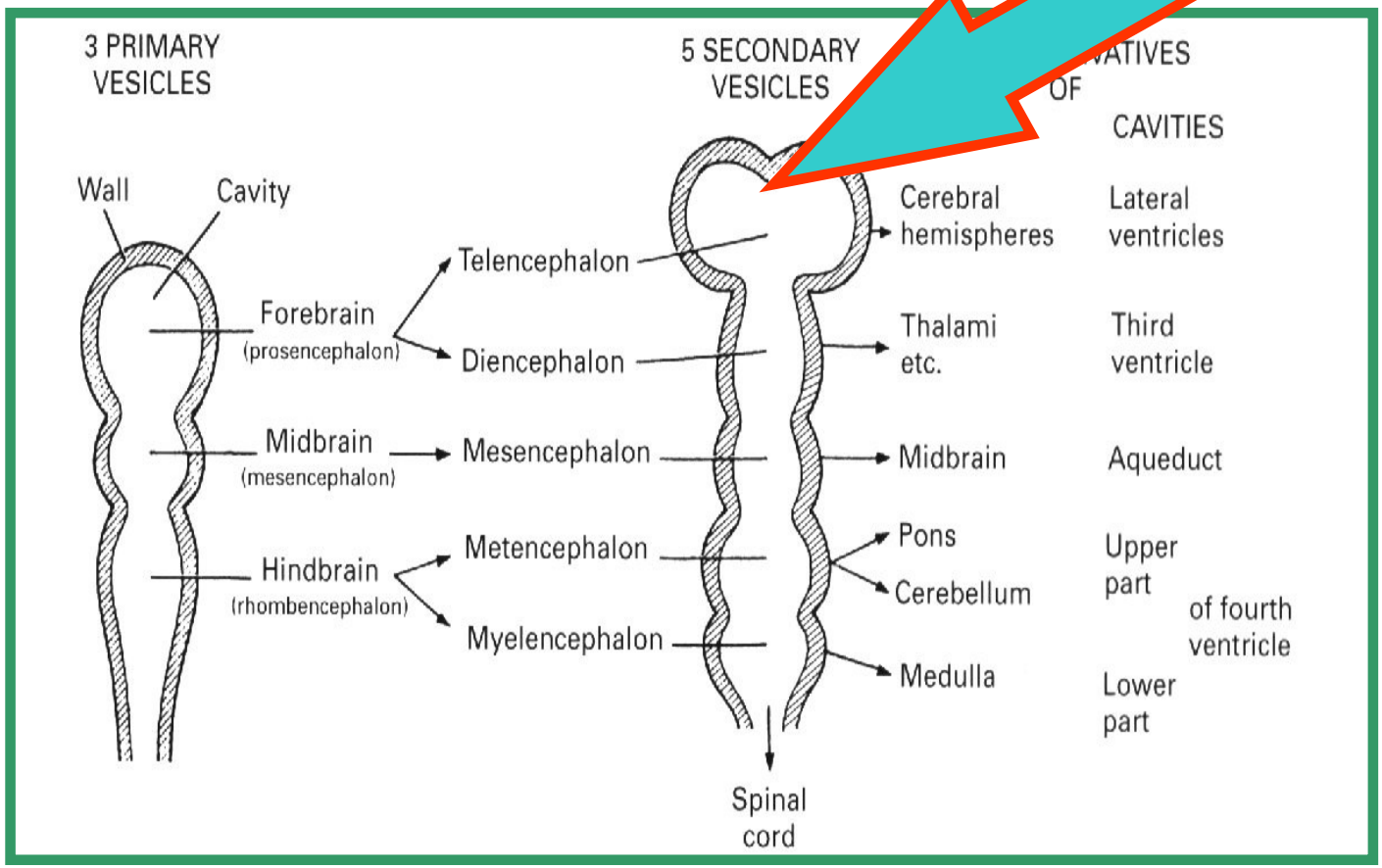


27-29 gg. 4 settimane

5-7 mm

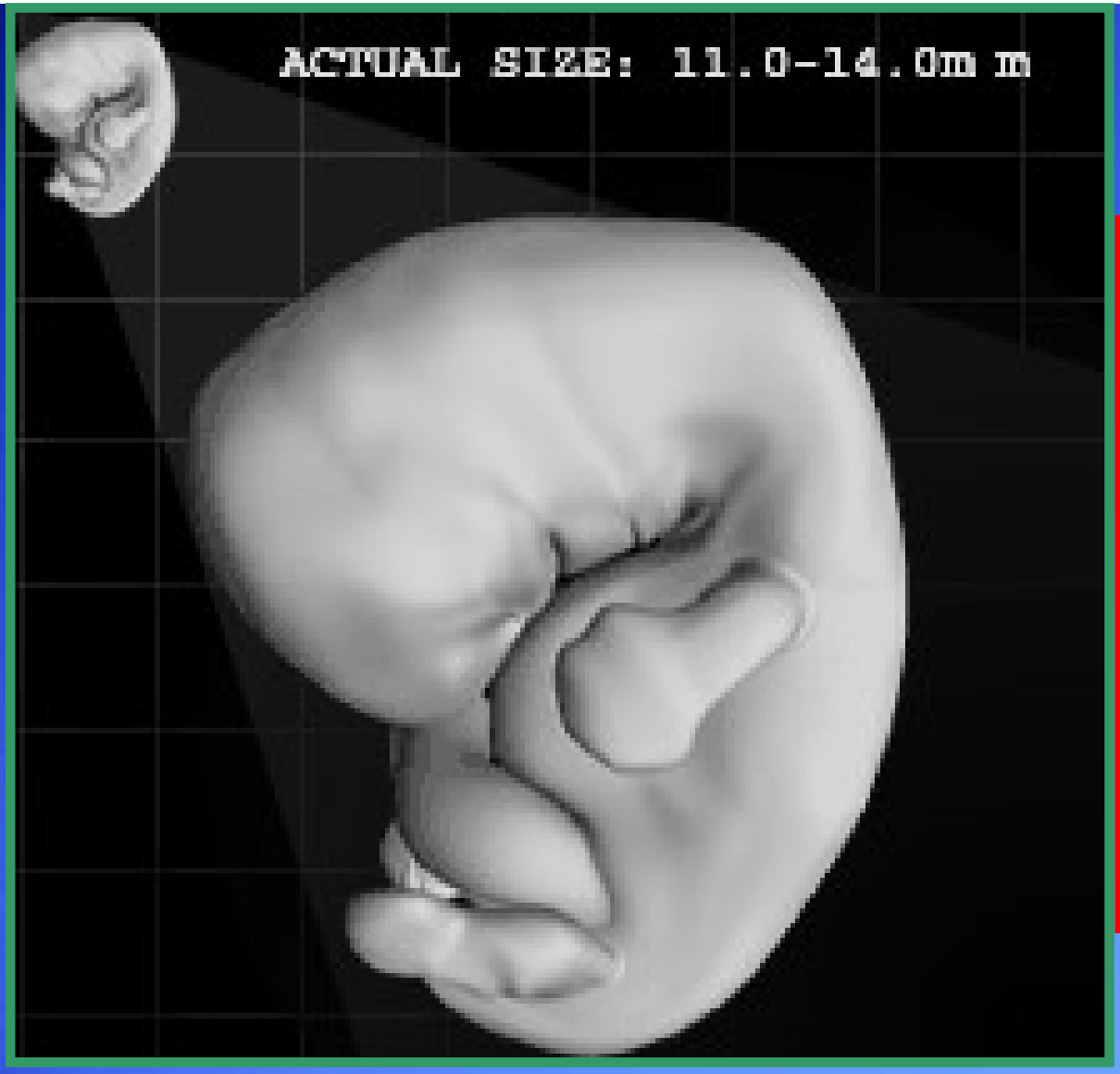
- ***Vescicole cerebrali primitive***
- Placode otico → Vescicola acustica → labirinto membranoso
- Retina
- Bocca, lingua
- Cuore– inizio sviluppo arco aortico
- Continua lo sviluppo delle gemme polmonari
- Sviluppo visceri addominali riconoscibili abbozzi di stomaco e pancreas, metanefro
- Gemme AA SS AA II
- Cute

Vescicole primitive



27-29 gg.

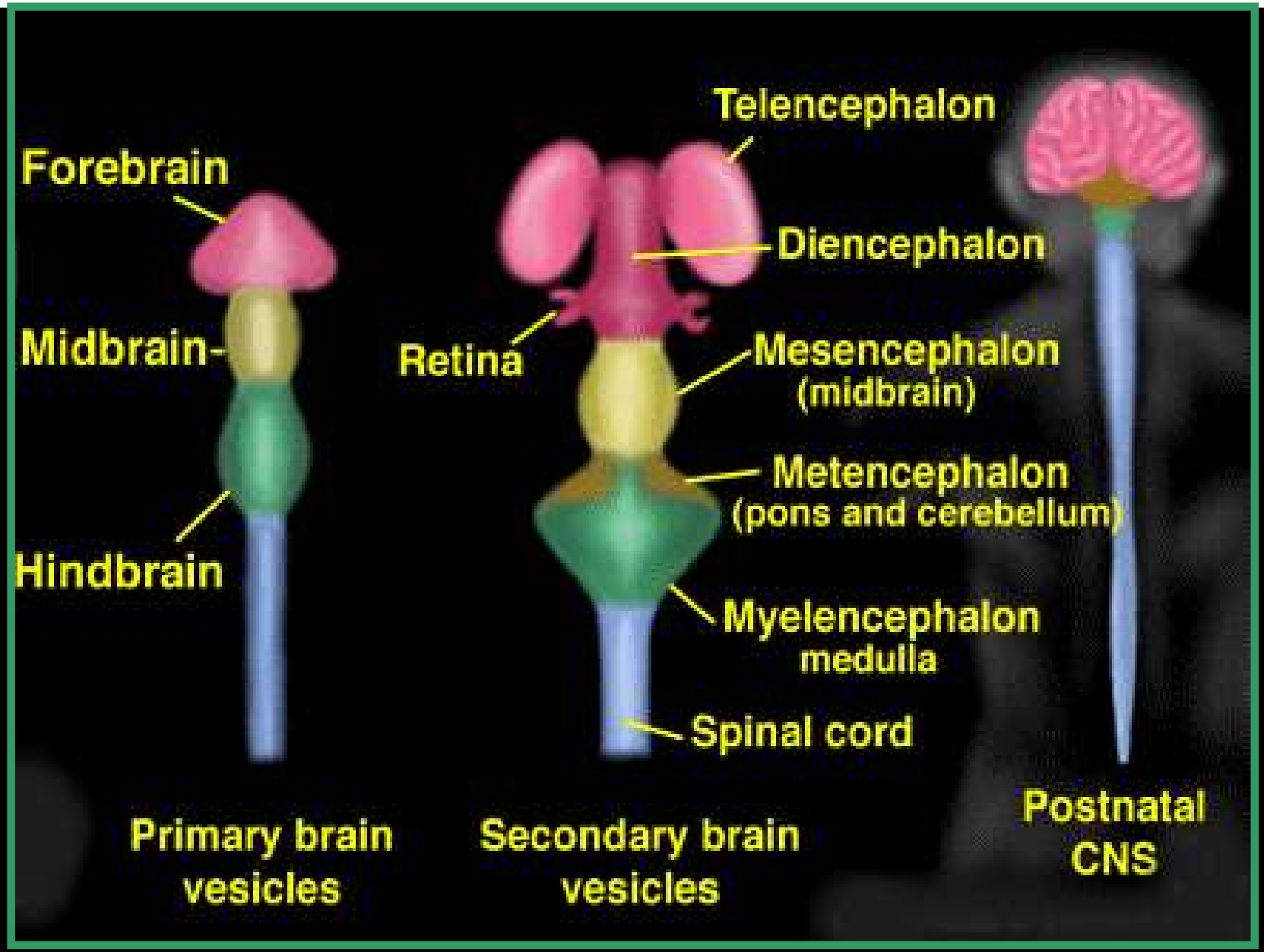
33-35 gg.



5 settimane

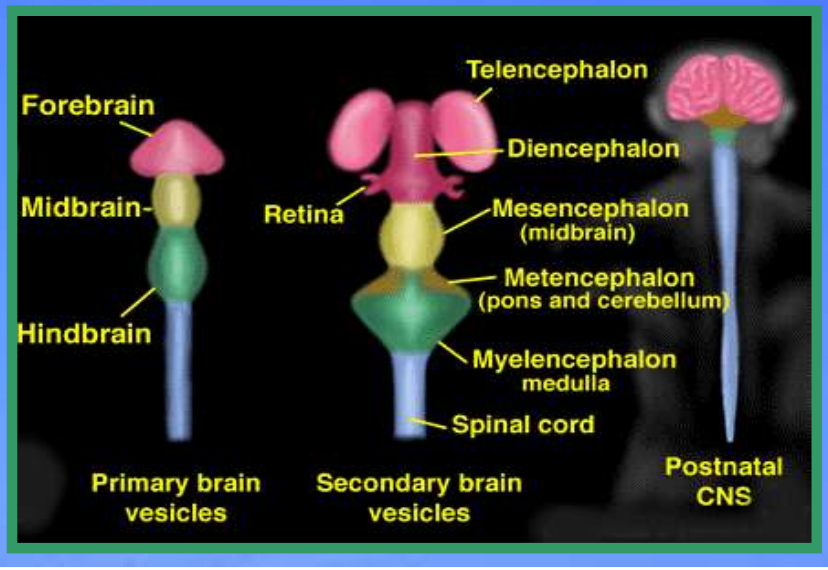
- **INIZIO INDUZIONE VENTRALE**

- Ossificazione scheletro
- Cuore Separazione Tronco della polmonare e Aorta
- Inizio produzione urine
- Tubercolo genitale
- Le braccia raggiungono la posizione finale
- Si riconosce il polso
- Prime incisure → dita


Forebrain
Midbrain
Hindbrain
Primary brain vesicles
Telencephalon
Diencephalon
Retina
Mesencephalon (midbrain)
Metencephalon (pons and cerebellum)
Myelencephalon medulla
Spinal cord
Secondary brain vesicles
Postnatal CNS

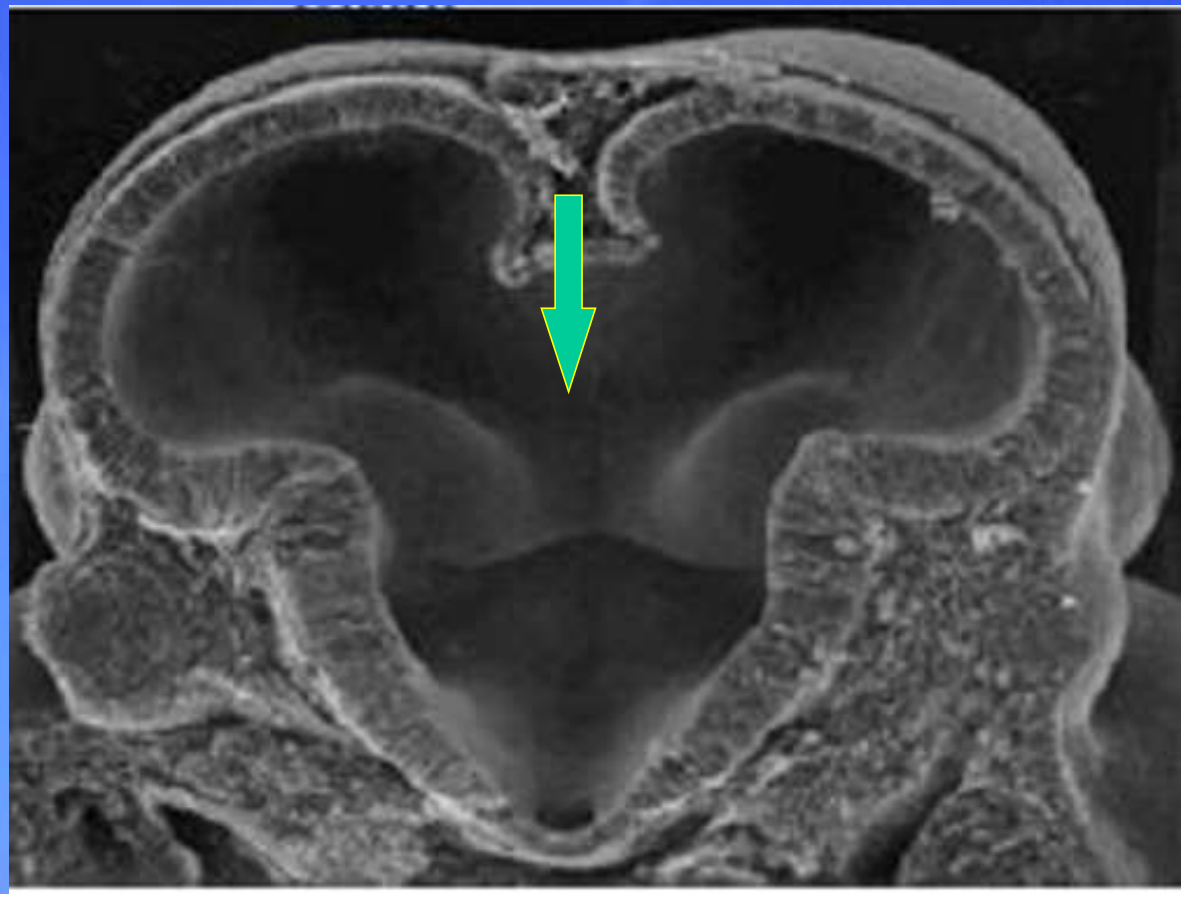
COMPLETAMENTO INDUZIONE VENTRALE

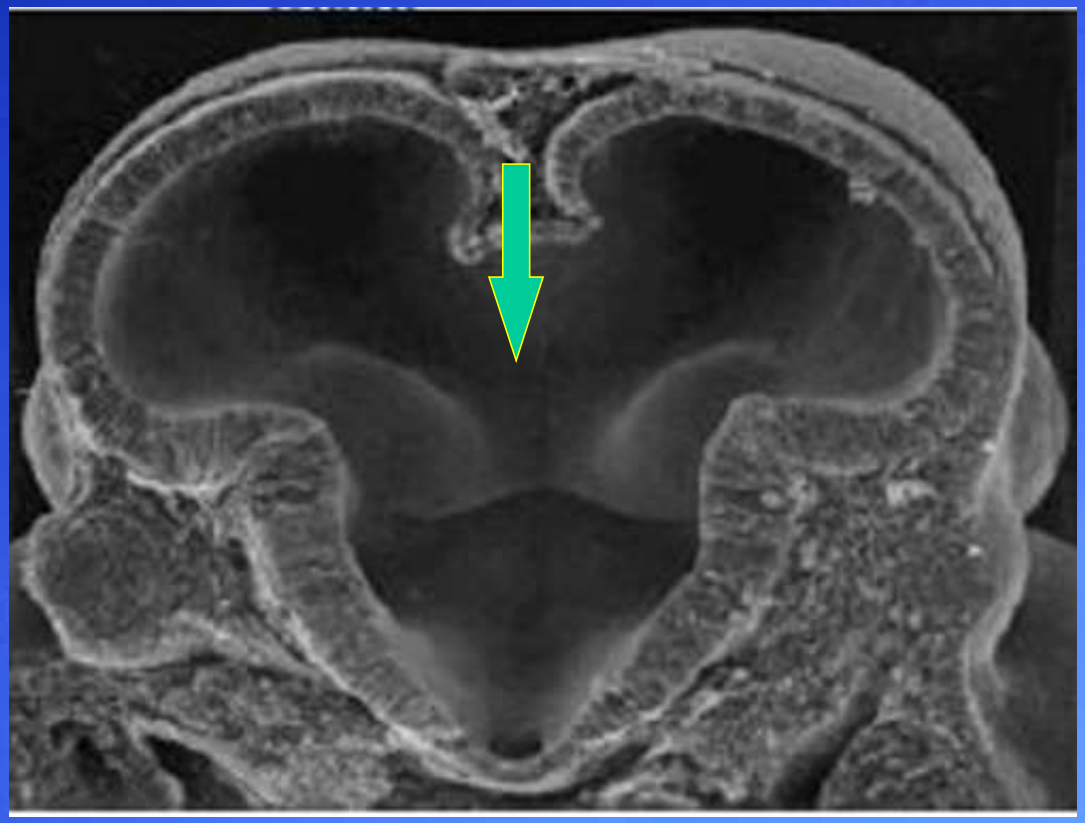
- Primi movimenti spontanei
- Narici e punta del naso sviluppati
- Si delineano le dita dei pied
- Membrana anale perforata
- Membrane urogenitali differenziate
- Testicoli ed ovaie distinguibili

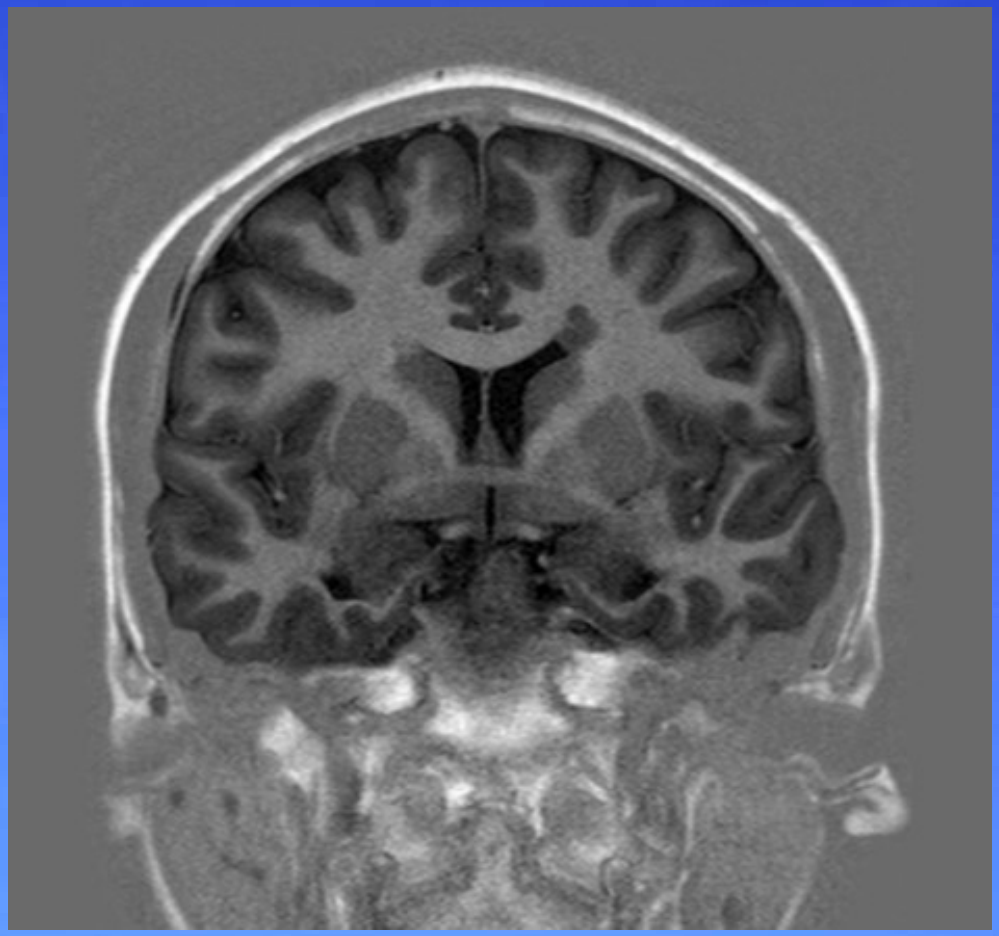


OLOPROSOENCEFALIA

- *Anomalia della induzione ventrale 25-29 gg (4 settimane)*
- *Il prosencefalo non da luogo al clivaggio in due emisferi*
- Si forma un ventricolo unico centrale fuso col terzo
- Da ipotelorismo a ciclopia
- Possibile assenza dell'ipofisi
- Frequente nelle trisomie







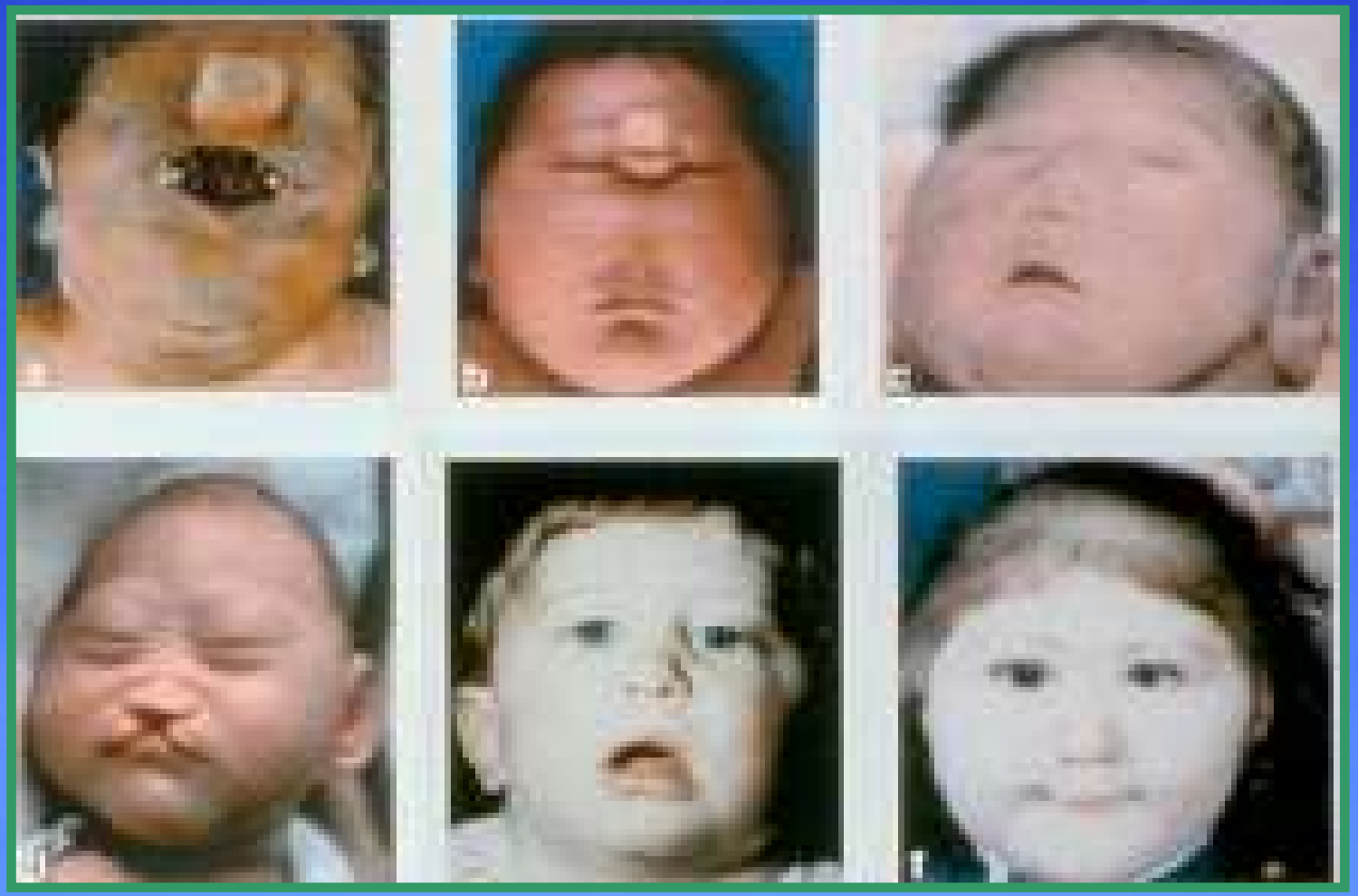
Fenotipi

Gravi

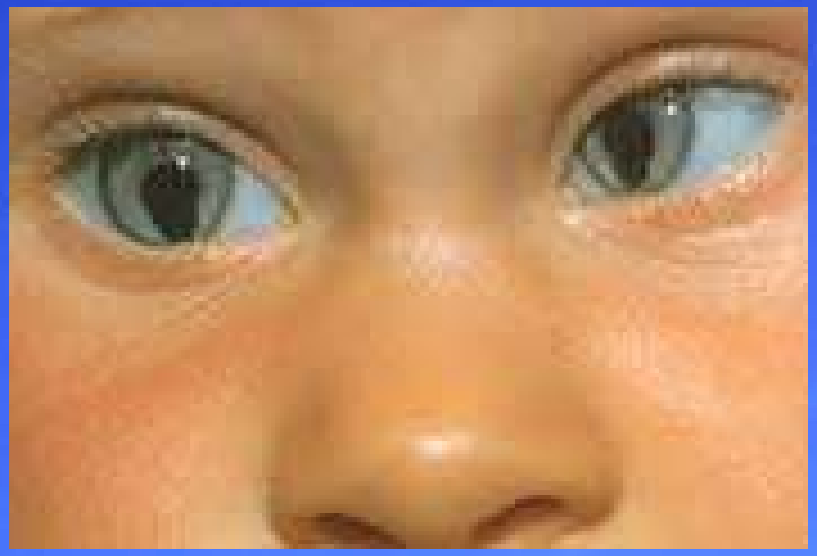
- Sinoftalmia
- Ciclopia
- Proboscide
- Cebocefalia (singola narice appiattita)
- Assenza di tratti riconoscibili

Lievi

- Labiopalatoschisi
- Ipoplasia mediofacciale
- Ipotelorismo
- Incisivo centrale unico



- Assenza del frenulo labiale superiore
- Incisivo unico
- Ipotelorismo
- Coloboma dell’iride,



Oloprosoencefalia	alobare	semilobare	lobare
Anomalie faciali	+ 83%	30% (labiopalatoschisi bila) ipertelorismo	minori o assenti
Circonferenza cranica	microcefefalia	microcefalia/trigonocefalia	
Disturbo termoregolazione	+		
Ass. sv.psm+auxologico	+	+	Disabilità intellettiva freq
Convulsioni	+		
Idrocefalo			+
life span	-	qualche anno	fino adulto→procreazione
Ventricoli laterali	Cavità unica	cavità a ferro di cavallo separazione c.occipitali	Separati solo in frontale no setto pellucido tetto dei ventricoli ipoplasia del C.C.
talami sezione coronale	fusi	fusi	
falce cervello	assente		
Scissura interemisferica	assente		
Sezione .sag.paramediana	cavità ventricolare a contatto con la volta ossea	Presenza di parenchima cerebrale	

Sindromi con oloprosoencefalia

- **Smith-Lemli-Opitz syndrome** https://omim.org/entry/270400
- **Steinfeld syndrome**
- **Zellweger syndrome**
- **Varadi syndrome**
- **Kallman syndrome**
- **Aicardi syndrome**
- **Lambotte syndrome**
- **Agnathia-HPE association**
- **Pallister-Hall syndrome**
- **Rubinstein-Taybi syndrome**
- **Hydrolethalus syndrome**
- **Meckel syndrome**
- **Walker-Warburg syndrome**
- **Majewski syndrome**
- **Di George syndrome del 22q11.2**

Zellweger syndrome: malattia dei perossisomi deficit di catalasi

1: # 214100. PEROXISOME BIOGENESIS DISORDER 1A (ZELLWEGER); PBD1A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 1, INCLUDED; CG1, INCLUDED
Cytogenetic location: 7q21.2
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

2: # 614870. PEROXISOME BIOGENESIS DISORDER 6A (ZELLWEGER); PBD6A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 7, INCLUDED; CG7, INCLUDED
Cytogenetic location: 1p36.32
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

3: # 614887. PEROXISOME BIOGENESIS DISORDER 13A (ZELLWEGER); PBD13A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP K, INCLUDED; CGK, INCLUDED
Cytogenetic location: 1p36.22
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

4: # 614876. PEROXISOME BIOGENESIS DISORDER 8A (ZELLWEGER); PBD8A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 8, INCLUDED; CG8, INCLUDED
Cytogenetic location: 11p11.2
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

5: # 614859. PEROXISOME BIOGENESIS DISORDER 3A (ZELLWEGER); PBD3A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 3, INCLUDED; CG3, INCLUDED
Cytogenetic location: 17q12
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

6: # 614866. PEROXISOME BIOGENESIS DISORDER 5A (ZELLWEGER); PBD5A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 5, INCLUDED; CG5, INCLUDED
Cytogenetic location: 8q21.13
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

7: # 614886. PEROXISOME BIOGENESIS DISORDER 12A (ZELLWEGER); PBD12A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 14, INCLUDED
Cytogenetic location: 1q23.2
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

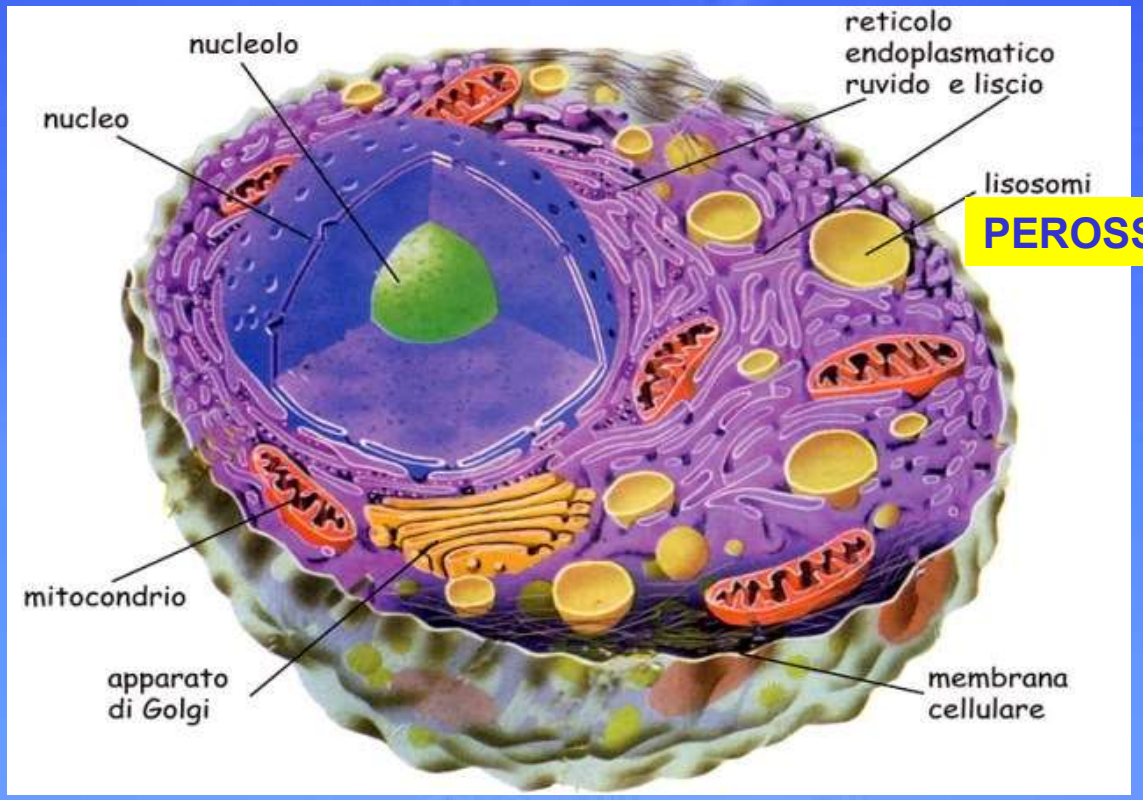
8: # 614872. PEROXISOME BIOGENESIS DISORDER 7A (ZELLWEGER); PBD7A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 8, INCLUDED; CG8, INCLUDED
Cytogenetic location: 22q11.21
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

9: # 614883. PEROXISOME BIOGENESIS DISORDER 11A (ZELLWEGER); PBD11A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 13, INCLUDED; CG13, INCLUDED
Cytogenetic location: 2p13
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

10: # 614882. PEROXISOME BIOGENESIS DISORDER 10A (ZELLWEGER); PBD10A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 12, INCLUDED; CG12, INCLUDED
Cytogenetic location: 6q24.2
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

11: # 614862. PEROXISOME BIOGENESIS DISORDER 4A (ZELLWEGER); PBD4A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 4, INCLUDED; CG4, INCLUDED
Cytogenetic location: 6p21.1
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links

12: # 214110. PEROXISOME BIOGENESIS DISORDER 2A (ZELLWEGER); PBD2A
PEROXISOME BIOGENESIS DISORDER, COMPLEMENTATION GROUP 2, INCLUDED; CG2, INCLUDED
Cytogenetic location: 12p13.31
Matching terms: (syndrome | syndromic), zellweger
► Phenotype-Gene Relationships ► Phenotypic Series ► ICD+ ► Links



PEROSSISOMA

ZELLWEGER

https://omim.org/entry/214100

NEUROLOGIC
Central Nervous System
-
- *Severe mental retardation*
  - *Hypotonia*
  - *Seizures*
  - *Hyporeflexia or areflexia*
  - *Polymicrogyria*
  - *Heterotopias/abnormal migration*
  - *Subependymal cysts*
  - *Agenesis/hypoplasia of corpus callosum*
  - *Hypoplastic olfactory lobes*
- - *Holoprosoencephaly*

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Emotional experience in parents of children with Zellweger spectrum disorders: A qualitative study

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[f] Department of Pediatrics, University of Nebraska Medical Center, University of Nebraska, 985940 Nebraska Medical Center – DRC II 4064, Omaha, NE 68198-5940, USA

Zellweger spectrum disorders (ZSDs) are rare, debilitating genetic diseases of peroxisome biogenesis that require constant management and lifelong care. Nevertheless, the experience of family caregivers for children diagnosed with ZSD is not well understood. In this study, we sought to characterize the emotional experience of ZSD family caregivers. Three 90-min focus groups were conducted with thirty-seven parents (25 mothers and 12 fathers) of children with ZSD during a family advocacy conference. Focus groups were arranged by age of proband (Group 1: 0–4 years, Group 2: 5–10 years, Group 3: > 11 years). Audio recordings of focus groups were transcribed and analyzed using software for coding purposes. Analyzed content was validated using peer debriefing, member checking, and method triangulation. Focus group results showed that nearly a third of ZSD caregivers described their overall emotional experience as a "rollercoaster." Additionally, three interconnected themes were identified: 1) range of emotions, 2) stressors, and 3) coping. Feeling overwhelmed and devastated were the most frequently described emotional responses. Corresponding stressors to these emotions included the burden of caregiver tasks associated with ZSD, and negative interactions with healthcare professionals. The most common coping strategies were acceptance of limitations of the diseases, redefining "normal" in the parenting experience, and advocating on behalf of the child and the patient community. This study underscores the profound emotional impact on parents who are caregivers for children with ZSDs, highlighting the utility of patient community feedback and qualitative approaches to fully characterize the overall family experience. Simple, targeted approaches focusing on improved communication between healthcare professionals and families, as well as offering resources for emotional support may greatly improve the lives of families living with ZSD and other rare pediatric diseases.

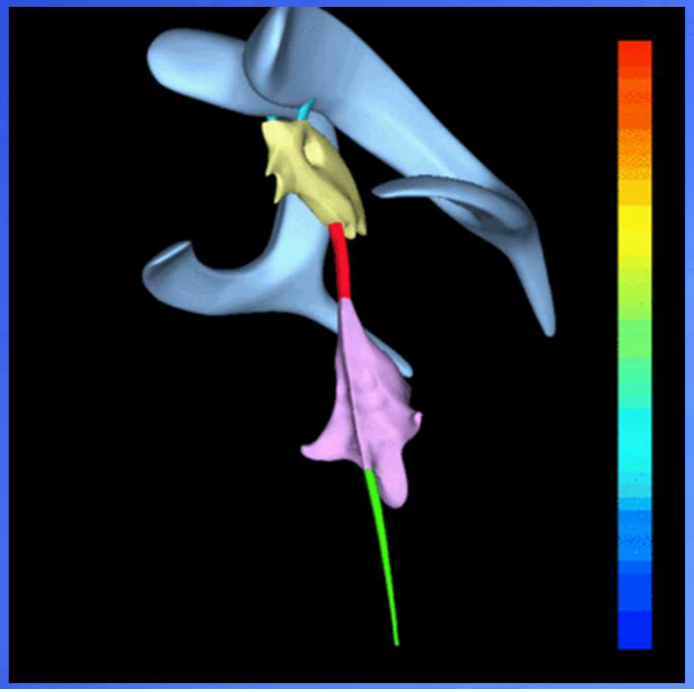
Accettazione della condizione

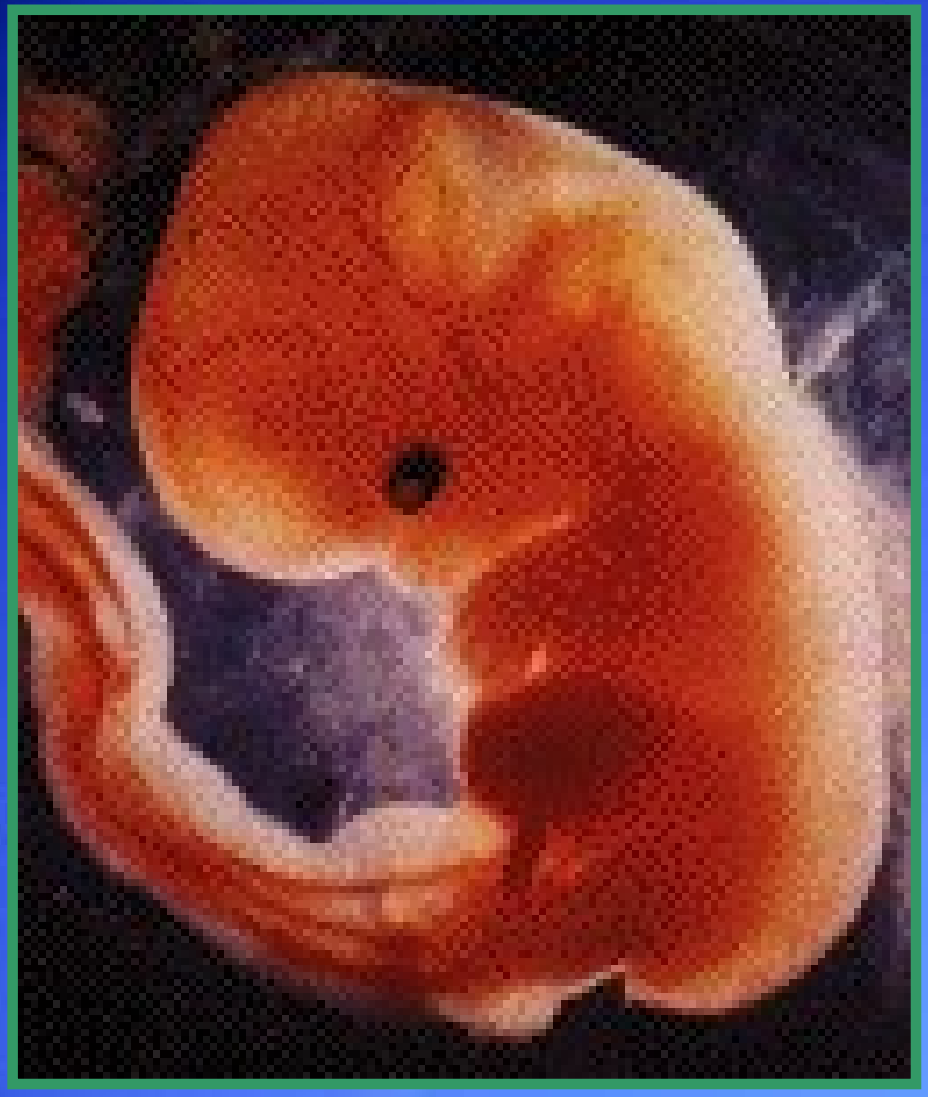
Ridefinizione di normalità esperienza genitoriale

Difesa dei diritti del bambino

Approccio ACT

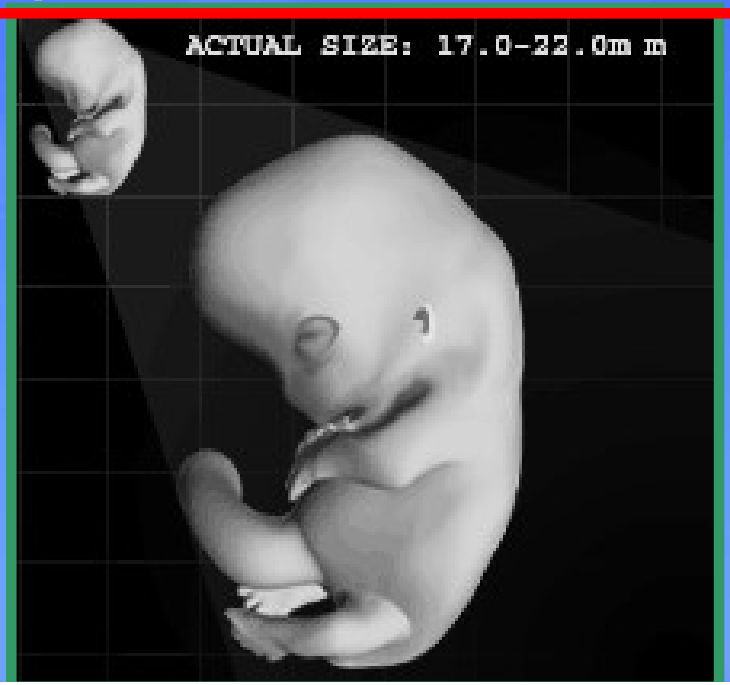
- **6 sett**
- **Comparsa del sistema ventricolare**
  spazi subaracnoidei
- 13 sett definizione del ventricolo laterale
- 21 sett fessura corioidea
- 32 sett striato





7 sett.

- Occhi localizzati ai lati della testa
- Orecchie basso impianto
- Intestino inizia a migrare verso l'embrione all'interno del cordone ombelicale
- Dita delle mani si allungano
- Le mani posturalmente si uniscono sull'addome
- Piedi palmati



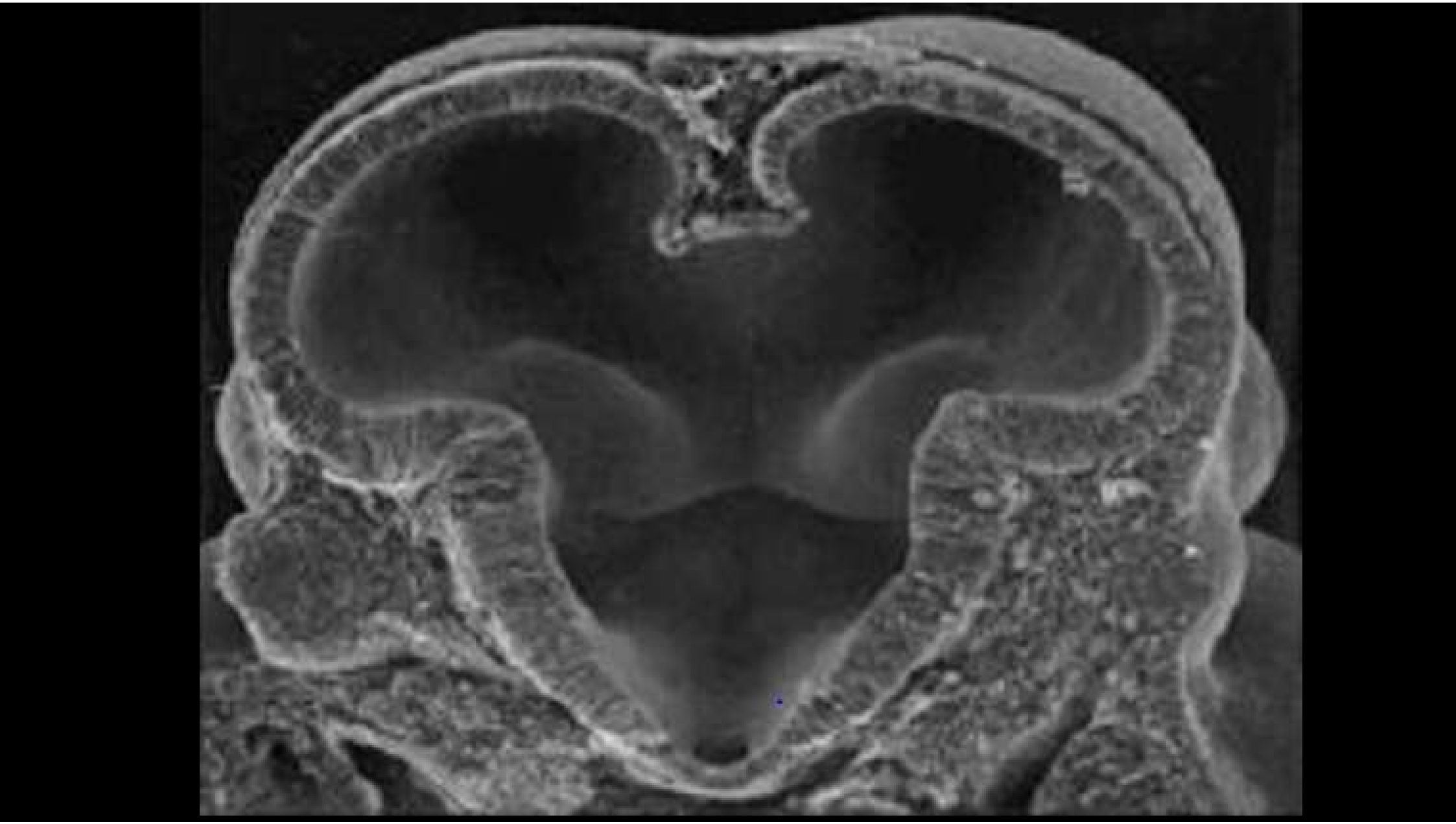
8 settimane

- Testa eretta e di forma rotonda
- Orecchie esterne sviluppate.
- Occhi chiusi, ma la retina è pigmentata
- Le palpebre cominciano a chiudersi.
- Si formano le papille gustative sulla lingua
- Inizio della fusione delle ossa del palato
- Si riconoscono le dita mani e piedi
- L'ectoderma è sostituito da un sottile strato di pelle

56-57 gg

12 sett- 3 mesi

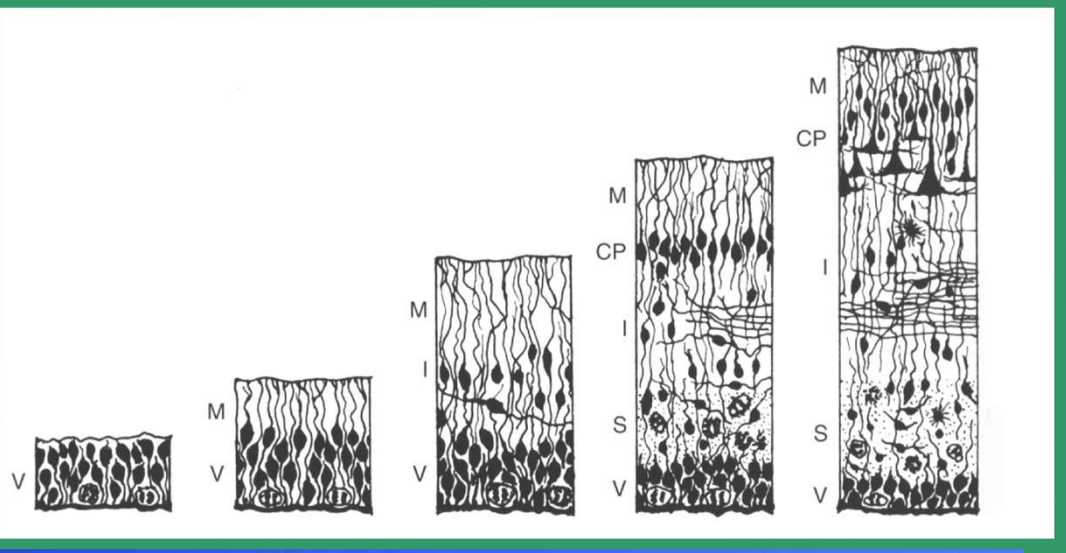
- 2-4 mesi difetti della proliferazione neuronale
- 3-5 mesi difetti della migrazione neuronale



Proliferazione neuronale 2-4 mesi

- Tutti i neuroni e la glia derivano dalle zone germinative subependimali presenti nel S.N.C.
- Le unità proliferative sono prodotte da divisioni simmetriche delle cellule staminali
- Successivamente le unità proliferative aumentano per divisioni asimmetriche delle cellule prima della migrazione neuronale

- Sono presenti 2 ondate proliferative
  - a) neuronale 2-4 mese
  - b) gliale 5→ 12 mesi di vita ed oltre
- Una parte della proliferazione gliale ha luogo nel 1° periodo per dare origine alla glia radiale che è coinvolta nella migrazione neuronale
- Oltre al 4° mese la proliferazione coinvolge principalmente cellule dello strato granulare del cervelletto e dell' ippocampo
- La proliferazione segue un modello "va e vieni" «migrazione nucleare intercinetica»



Zone cerebrali

M marginale

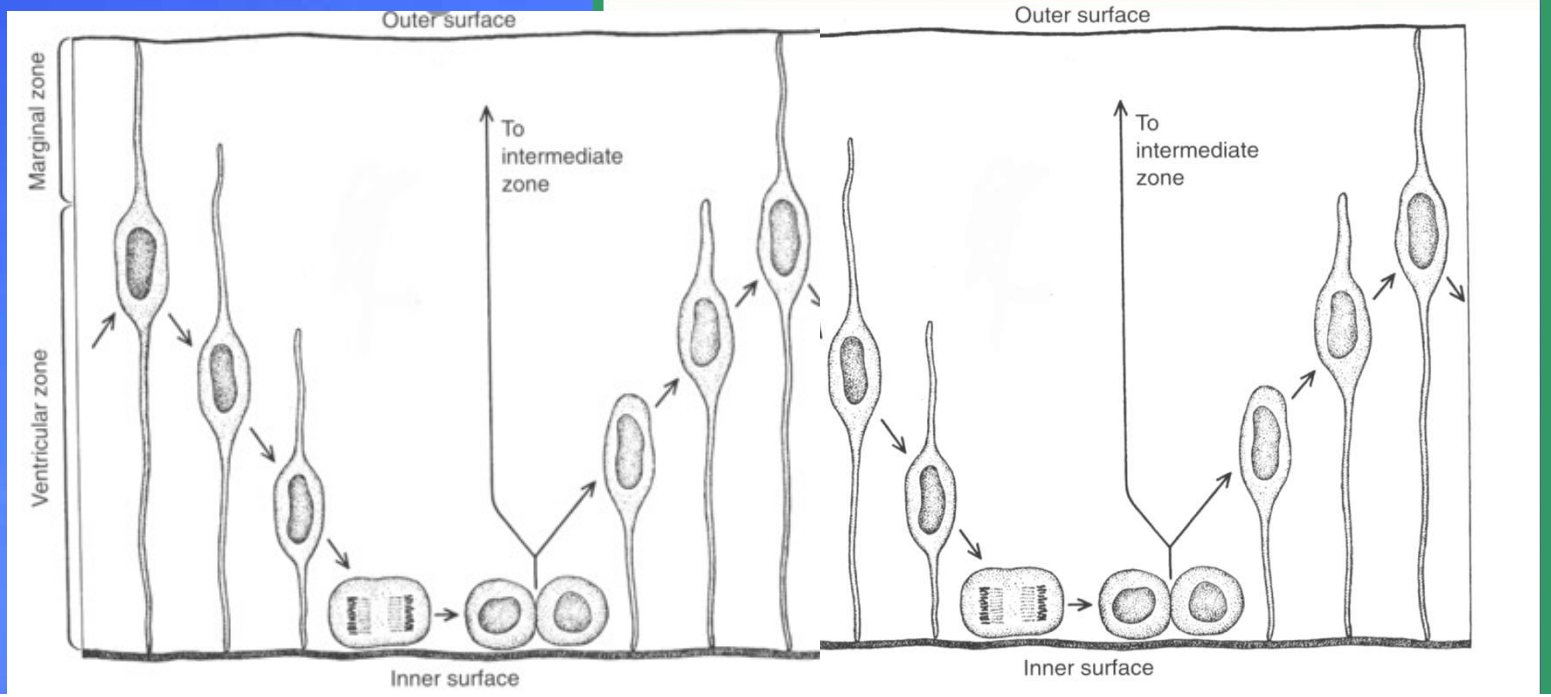
CP piatto corticale

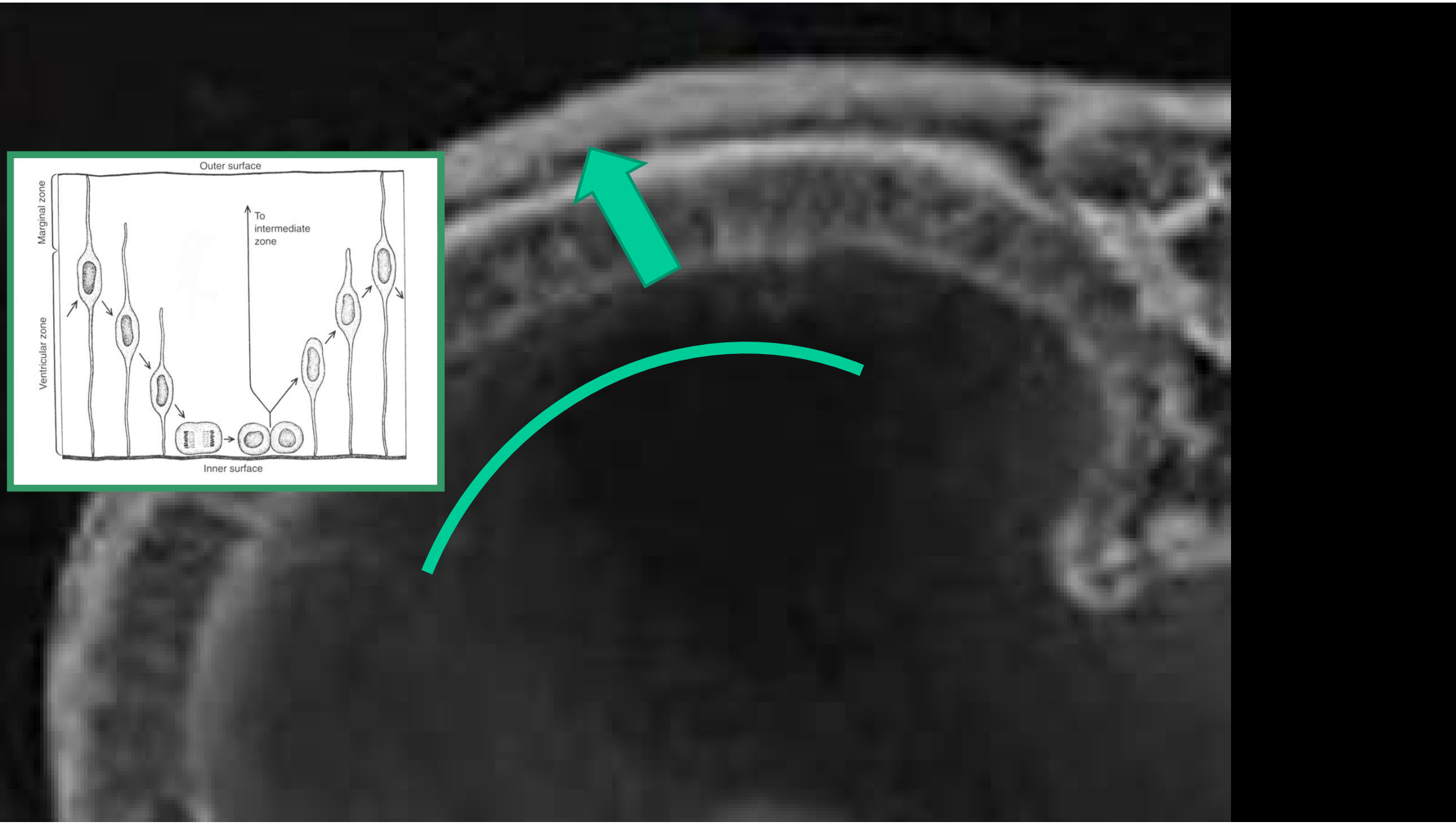
I intermedia

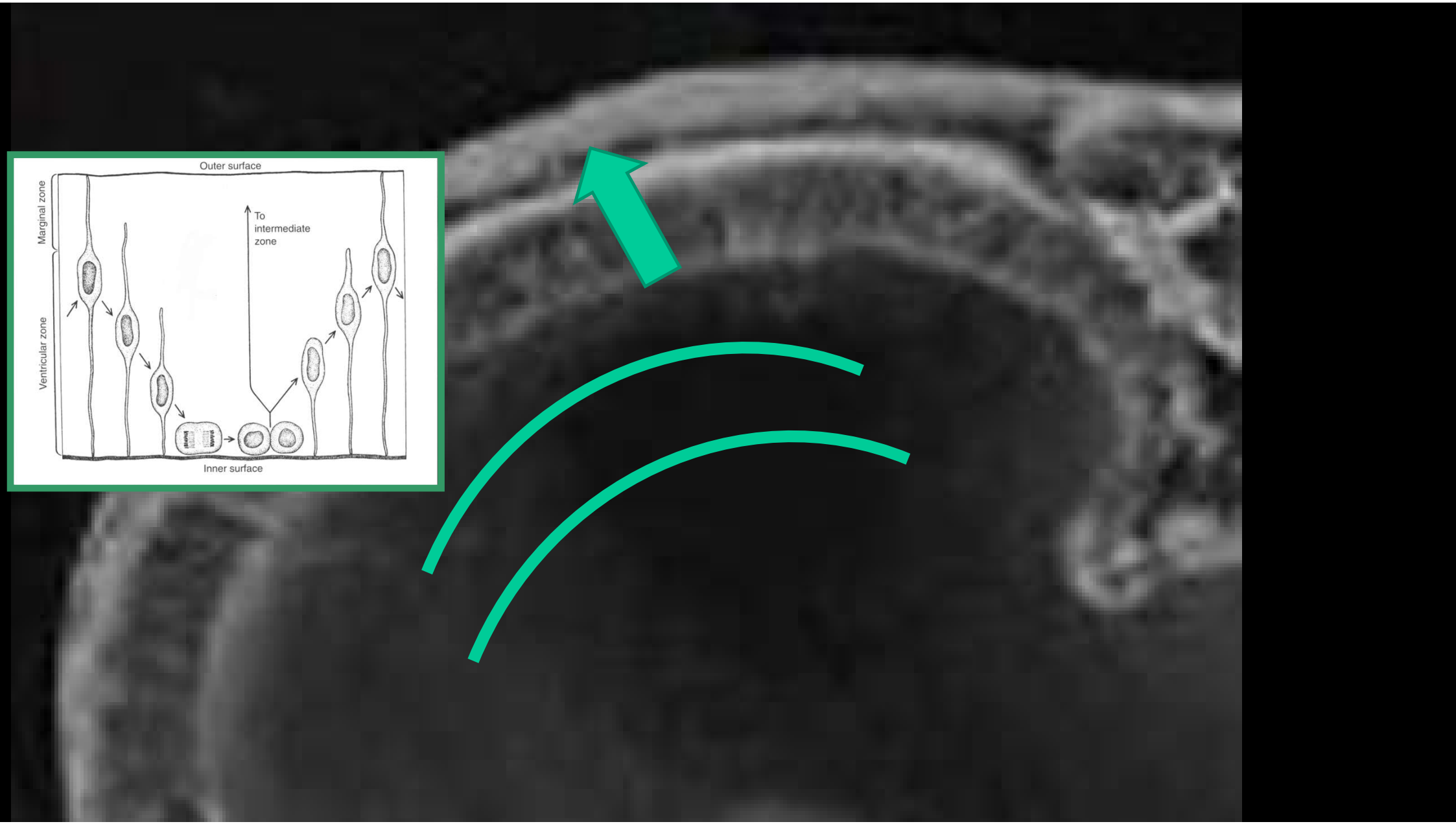
S sub ventr.

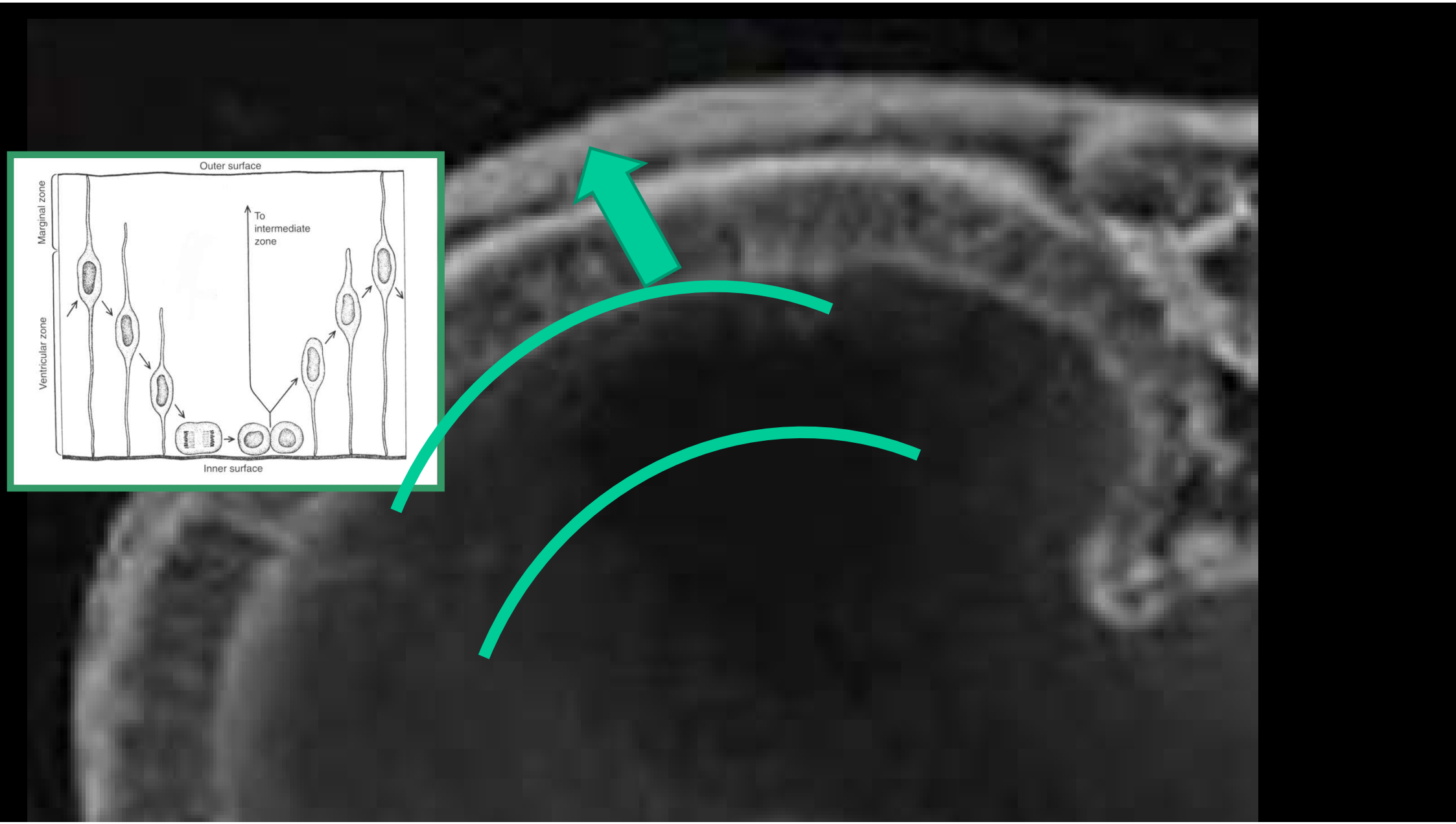
V ventricolare

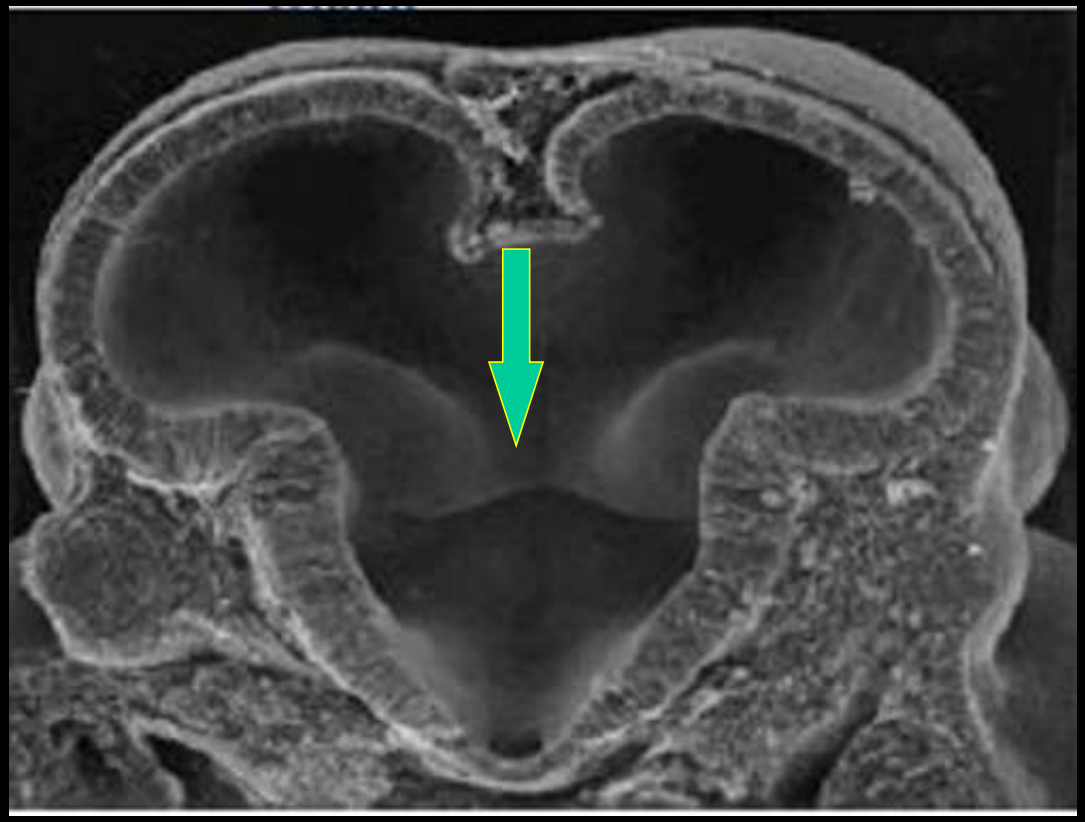
Eventi proliferativi nella zona ventricolare

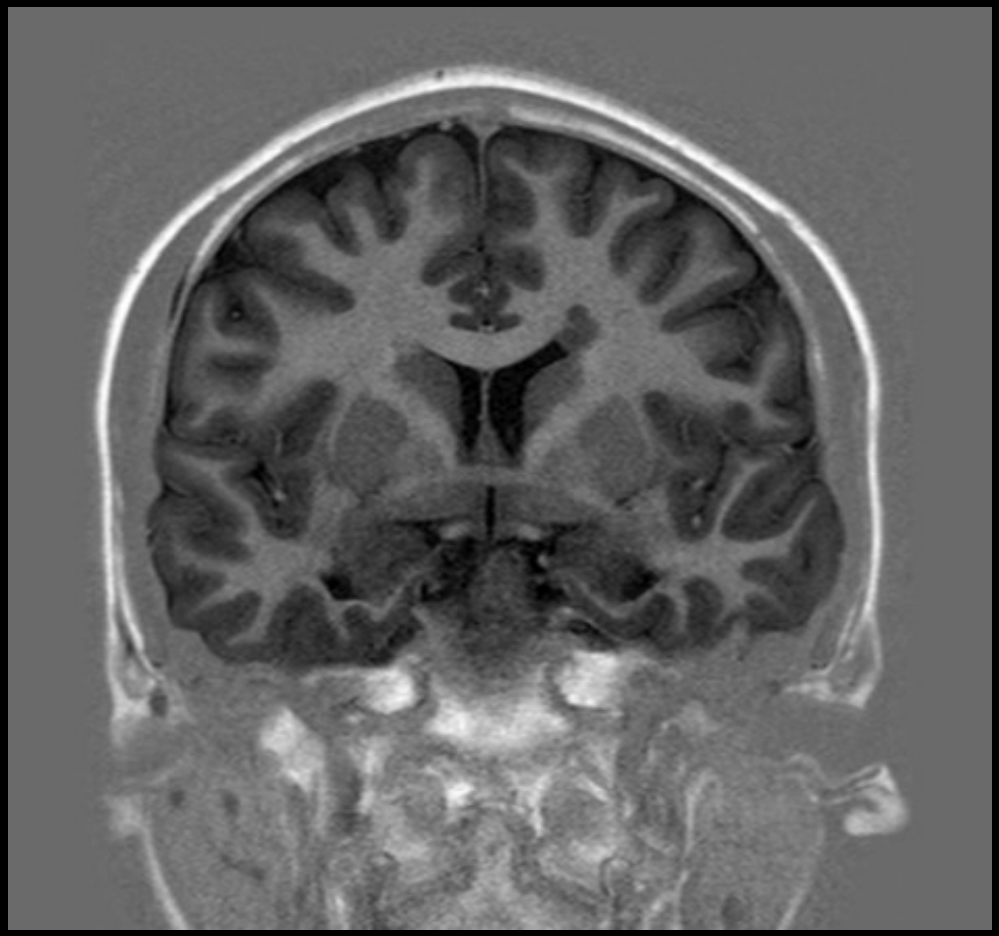


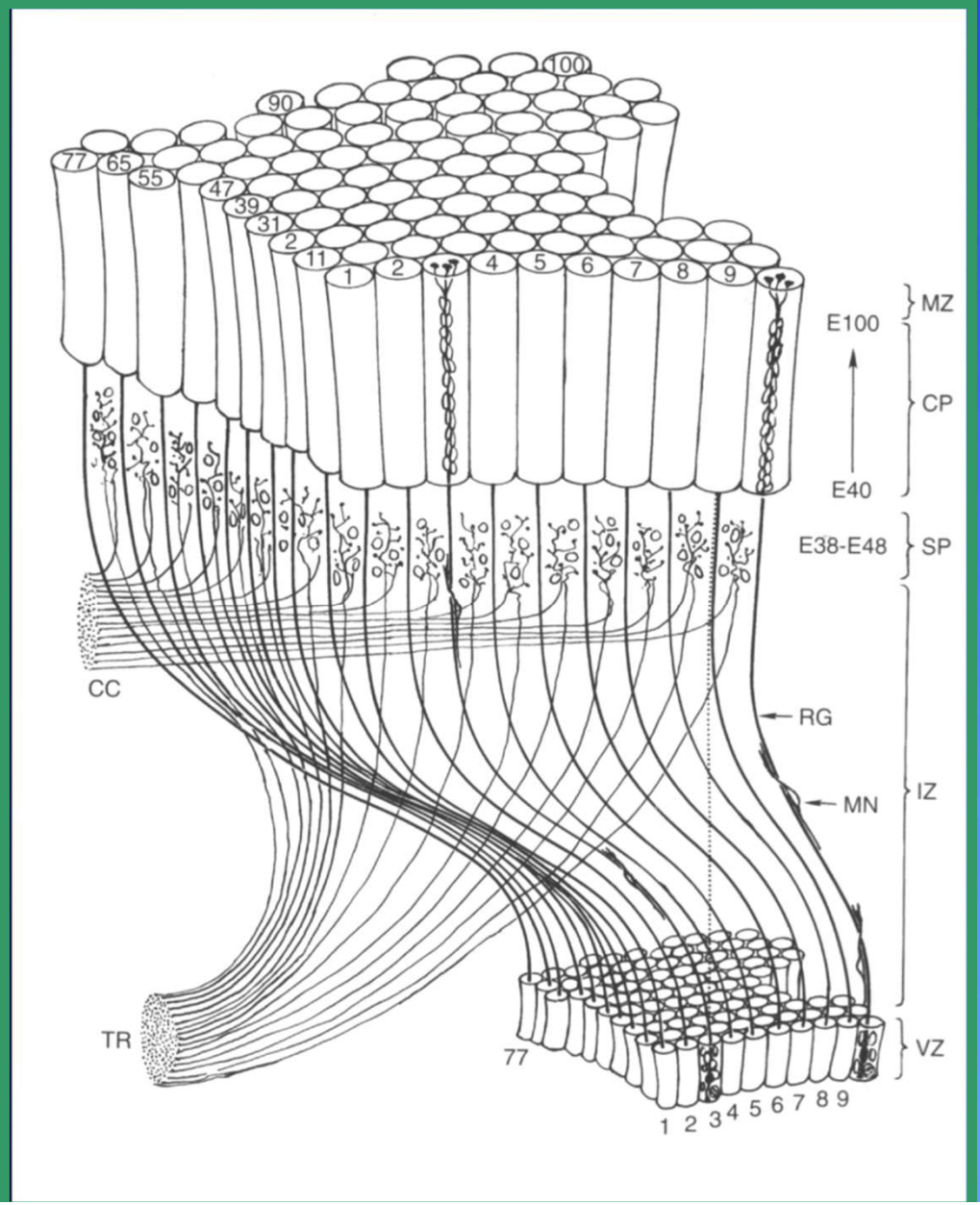

Outer surface
Marginal zone
To
intermediate
zone
Ventricular zone
Inner surface


Outer surface
Marginal zone
Ventricular zone
To
intermediate
zone
Inner surface

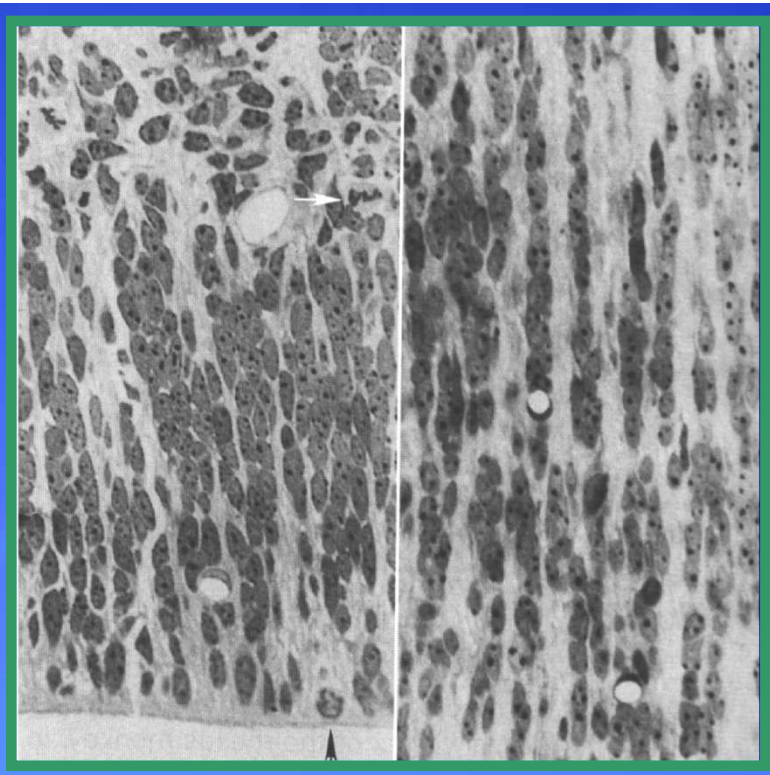

Outer surface
Marginal zone
To
intermediate
zone
Ventricular zone
Inner surface



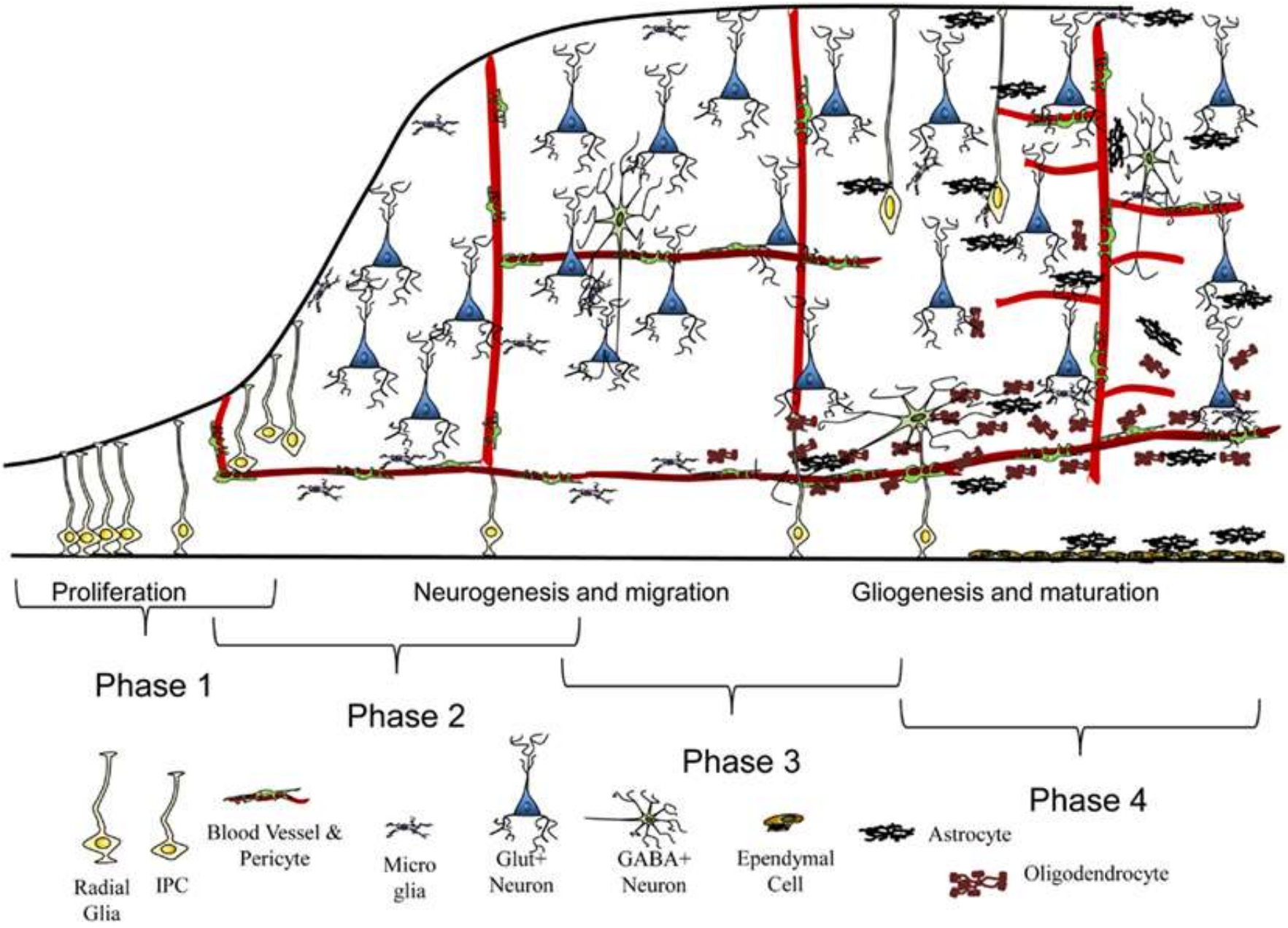


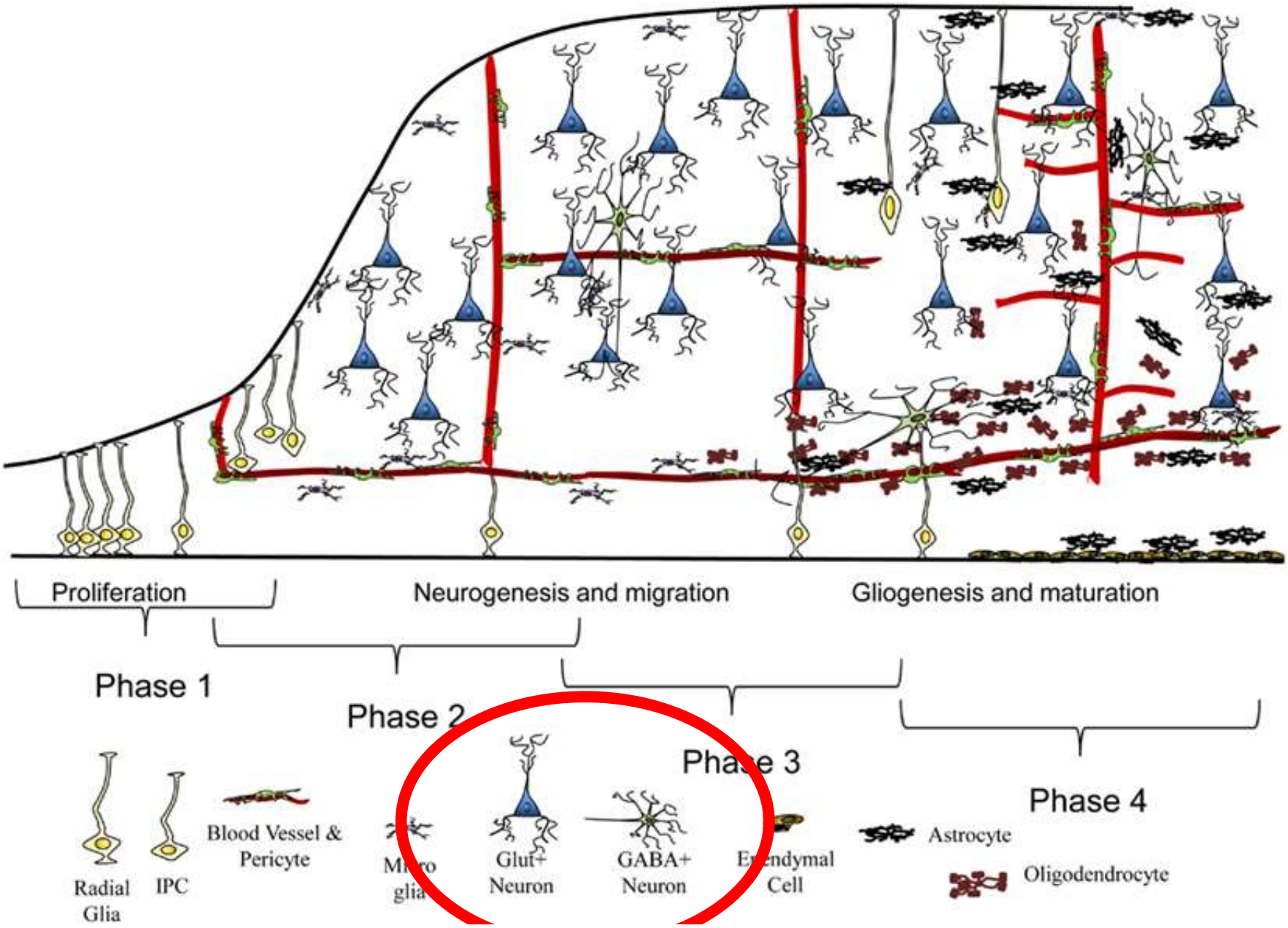


Relazioni tra zona germinativa e organizzazione della corteccia

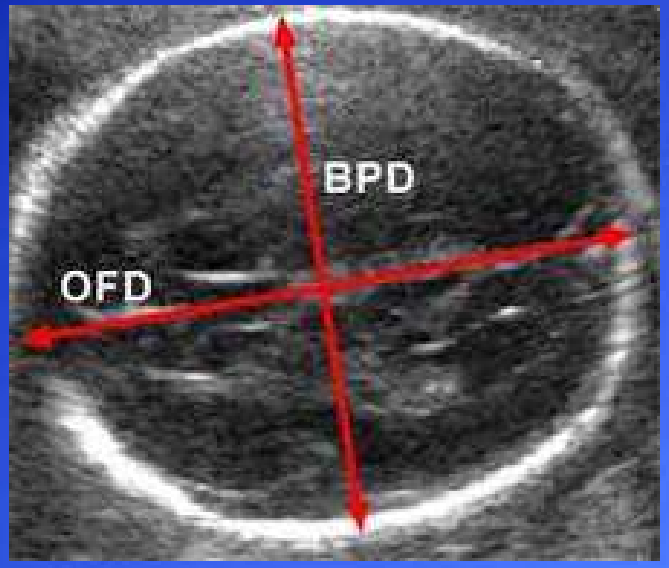


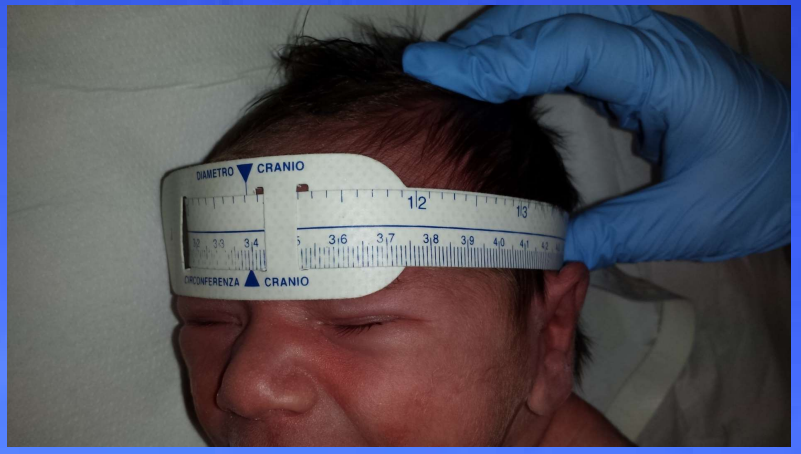
Colonne ontogenetiche composte da neuroni migranti


Proliferation
Neurogenesis and migration
Gliogenesis and maturation
Phase 1
Phase 2
Phase 3
Phase 4
Radial Glia
IPC
Blood Vessel & Pericyte
Micro glia
Glut+ Neuron
GABA+ Neuron
Ependymal Cell
Astrocyte
Oligodendrocyte


Proliferation
Neurogenesis and migration
Gliogenesis and maturation
Phase 1
Phase 2
Phase 3
Phase 4
Radial Glia
IPC
Blood Vessel & Pericyte
Glut+ Neuron
GABA+ Neuron
Astrocyte
Oligodendrocyte

La circonferenza cranica





La c.c. reale andrebbe misurata con craniometro e non metro da sarta!

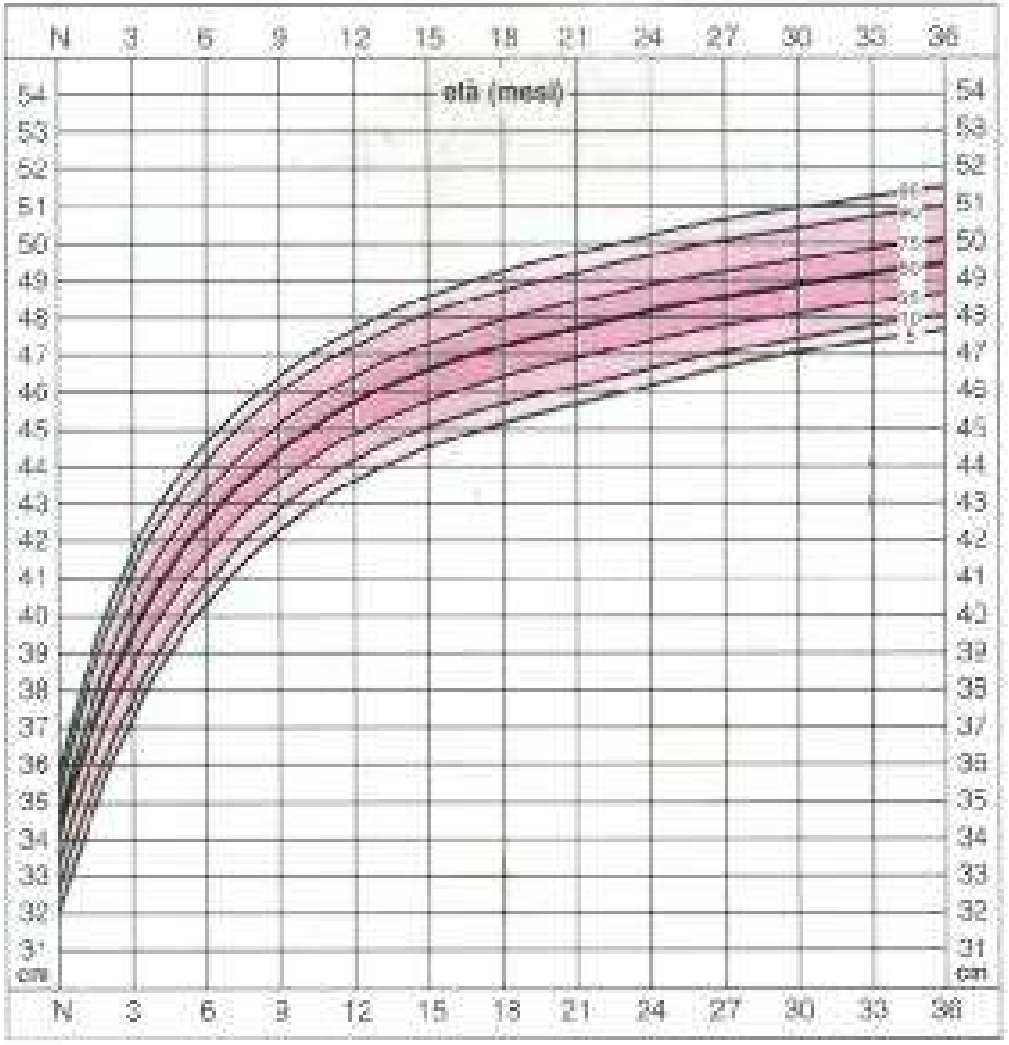
Il valore più attendibile è a 72 ore (eventualmente alla dimissione) soprattutto se in nato da parto spontaneo e con impegno prolungato della parte presentata

Si dovrebbe fare una media di 3 misurazione consecutive

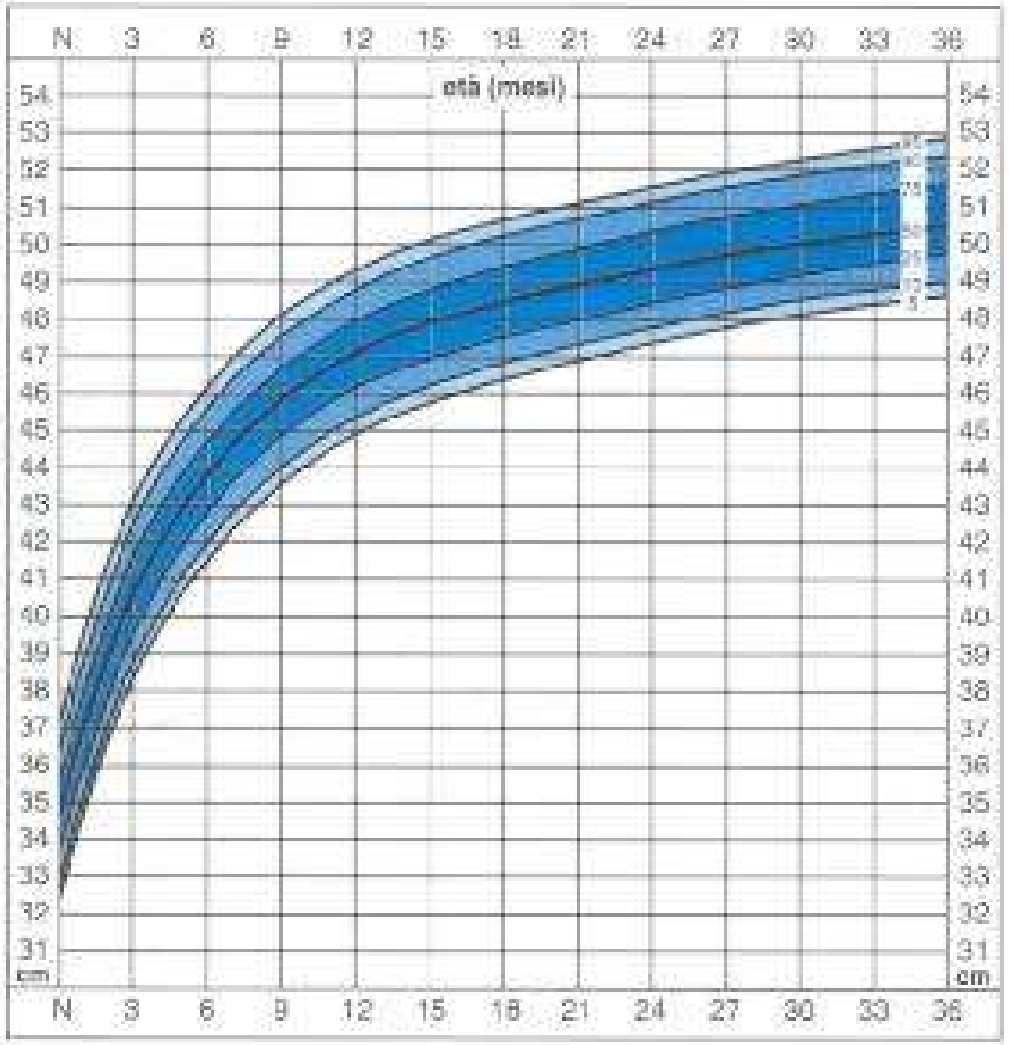
Altrimenti rischio di falso positivo per microcefalia elevato

Basarsi sempre sulla eventuale familiarità per il follow-up

Idem per le macrocefalie, che potrebbero slatentizzarsi nelle ore successive al parto (falso negativo)

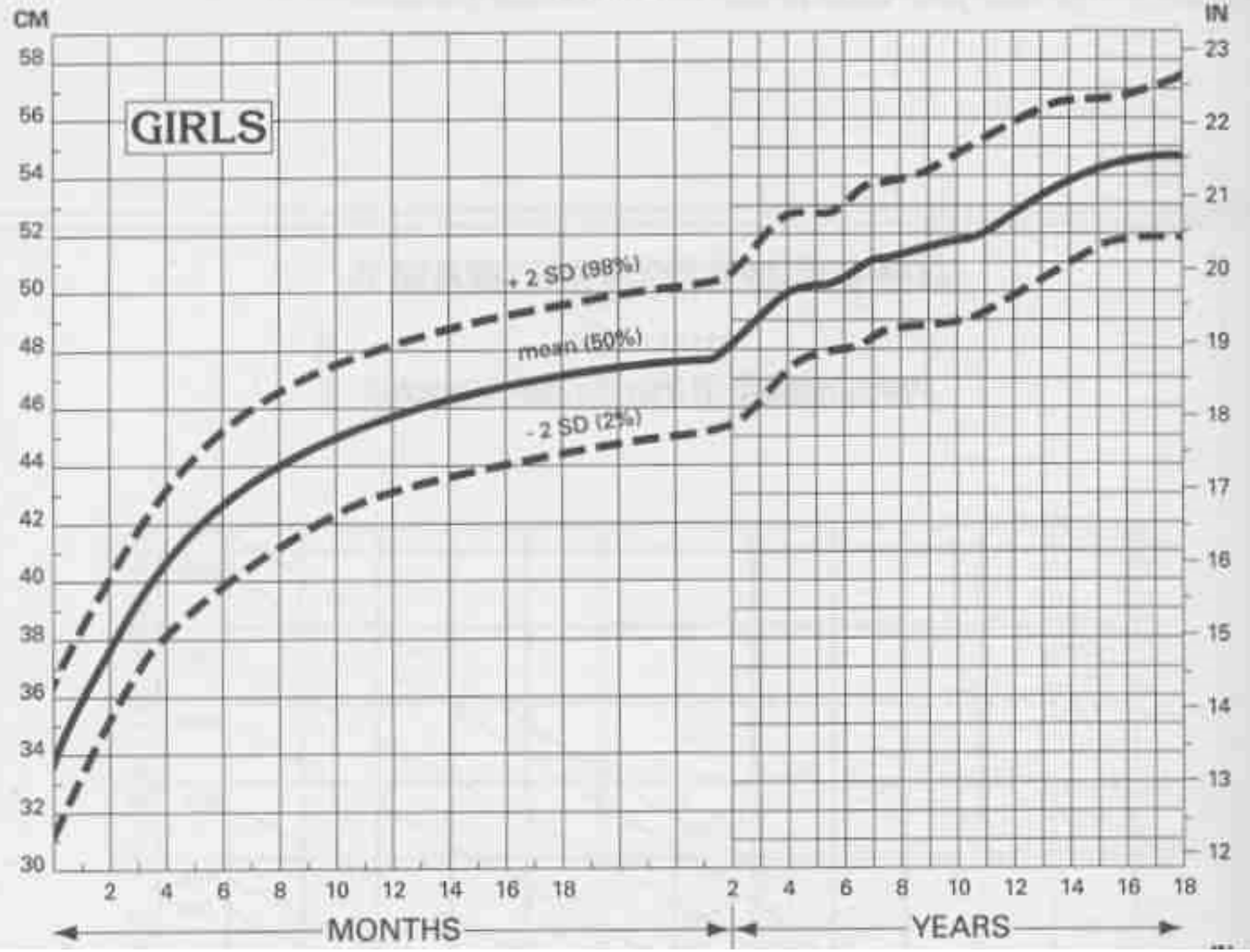


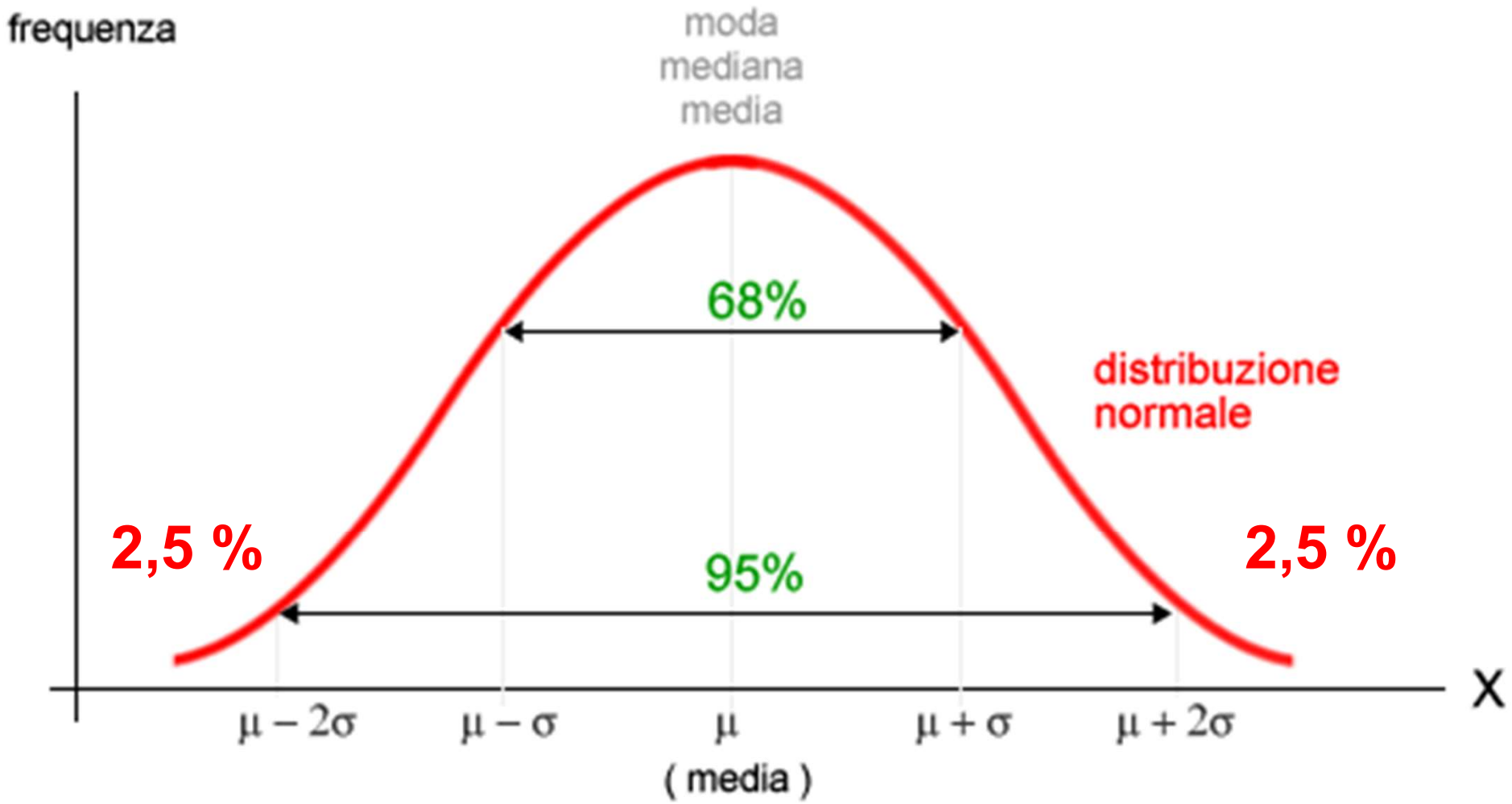
età (mesi)



età (mesi)

HEAD CIRCUMFERENCE CHARTS




frequenza
moda
mediana
media
68%
distribuzione
normale
2,5 %
95%
2,5 %
X
μ − 2σ
μ − σ
μ
μ + σ
μ + 2σ
(media)

Microcefalia Ipotesi:

- Anomalie cromosomiche
- Sindromi genetiche
- Tossine /virus → precoce differenziazione ependima→ arresto della attività mitotica del neuroepitelio telencefalico
- Irradiazione (4-20 seg)
- Farmaci (cortisone,aminopterina)
- Iperfenilalanimemia materna

Approccio clinico

- Definire la entità in DS e non centili
- Familiarità
- Reperto isolato o in un quadro sospetto per patologia genetica, infettiva prenatale
- Presente alla nascita o esordio successivo
- Anamnesi gravidica, perinatale e post natale
- Imaging prenatale e neonatale (tutti i neonati microcranici dovrebbero eseguire eco-doppler cerebrale)
- Compromissione organi di senso
- Presenza di segni neurologici-ritardo dello sviluppo-Disabilità intellettiva

MICROCEFALIA

- **1. Congenital**

- Isolated
- Familial (Autosomal recessive) microcephaly
- Autosomal Dominant microcephaly
- X-linked microcephaly
- Chromosomal (balanced rearrangements & Ring chromosome)

- Syndromes

- Chromosomal
- Down syndrome
- Edward Syndrome
- Patau Syndrome
- Unbalanced rearrangements
- Contiguous gene deletion
- 4p deletion (Wolf–Hirschhorn syndrome)
- 5p deletion (Cri-du-chat)
- 7q11.23 deletion (Williams syndrome)
- 22q11 deletion (DiGeorge syndrome)
- Single gene defects
- Smith–Lemli–Opitz syndrome
- Seckel syndrome
- Cornelia de Lange syndrome
- Holoprosencephaly

- Acquired
  - Disruptive injuries
    - Ischemic stroke
    - Hemorrhagic stroke
  - Death of a monozygotic twin
  - Congenital Infections
    - Congenital cytomegalovirus infection
    - Toxoplasmosis
    - Congenital rubella syndrome
  - Drugs
    - Fetal hydantoin syndrome
    - Fetal alcohol syndrome
  - Other
    - Radiation exposure to mother
    - Maternal Malnutrition
    - Maternal Phenylketonuria
    - Poorly controlled Gestational diabetes
    - Hyperthermia
    - Maternal Hypothyroidism
    - Placental insufficiency

•2. Postnatal onset

•Genetic

•Inborn errors of metabolism
•Congenital disorder of glycosylation
•Mitochondrial disorders
•Peroxisomal disorder
•Glucose transporter defect
•Menkes disease
•Amino acidopathies
•Organic acidemia

•Syndromes

•Contiguous gene deletion
•17p13.3 deletion (Miller–Dieker syndrome)
•Single gene defects
•Rett syndrome (primarily girls)
•Nijmegen breakage syndrome
•X-linked lissencephaly with abnormal genitalia
•Aicardi–Goutières syndrome
•Ataxia telangiectasia
•Cohen syndrome
•Cockayne syndrome

•Acquired

•Disruptive injuries

- Traumatic brain injury
- Hypoxic-ischemic encephalopathy
- Ischemic stroke
- Hemorrhagic stroke

•Infections

- Congenital HIV encephalopathy
- Meningitis
- Encephalitis

- Toxins
- Lead poisoning
- Chronic renal failure
- Deprivation
- Hypothyroidism
- Anemia
- Congenital heart disease
- Malnutrition

- Fatta eccezione per le **craniosinostosi** una circonferenza cranica piccola è legata ad un iposviluppo cerebrale
- Microcefalia primaria se si instaura nei primi 7 mesi di vita fetale
- Microcefalia secondaria se negli ultimi 2 mesi o nel periodo perinatale