Erasmus MC
Universitair Medisch Centrum Rotterdam

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Teaching Course Budapest 2016

Behavioural., neuropsychological and psychiatric aspects of neurology

ABNORMAL DEVELOPMENT

RED FLAGS AND CLUES TO DIAGNOSIS

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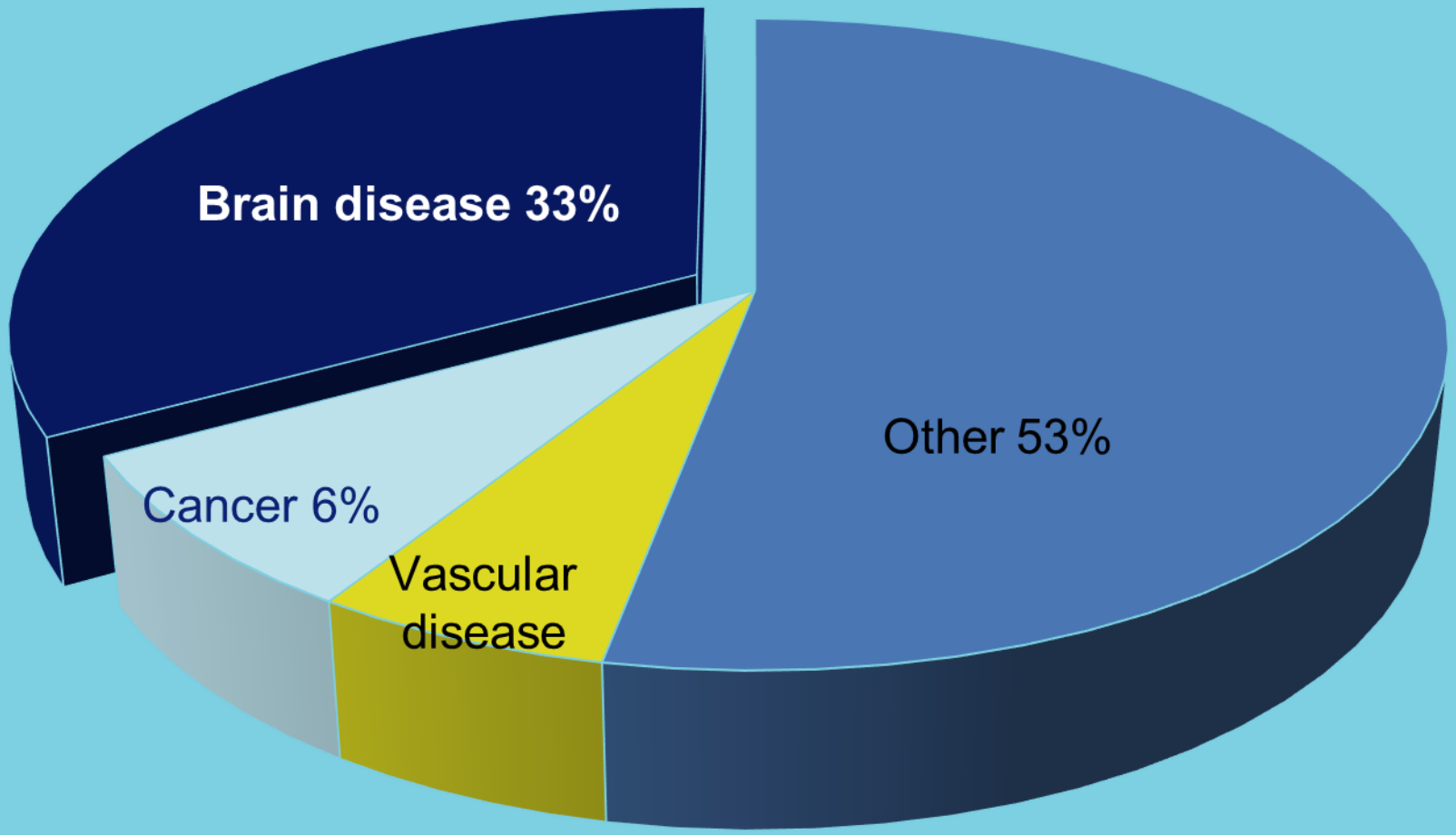
Financial burden to society



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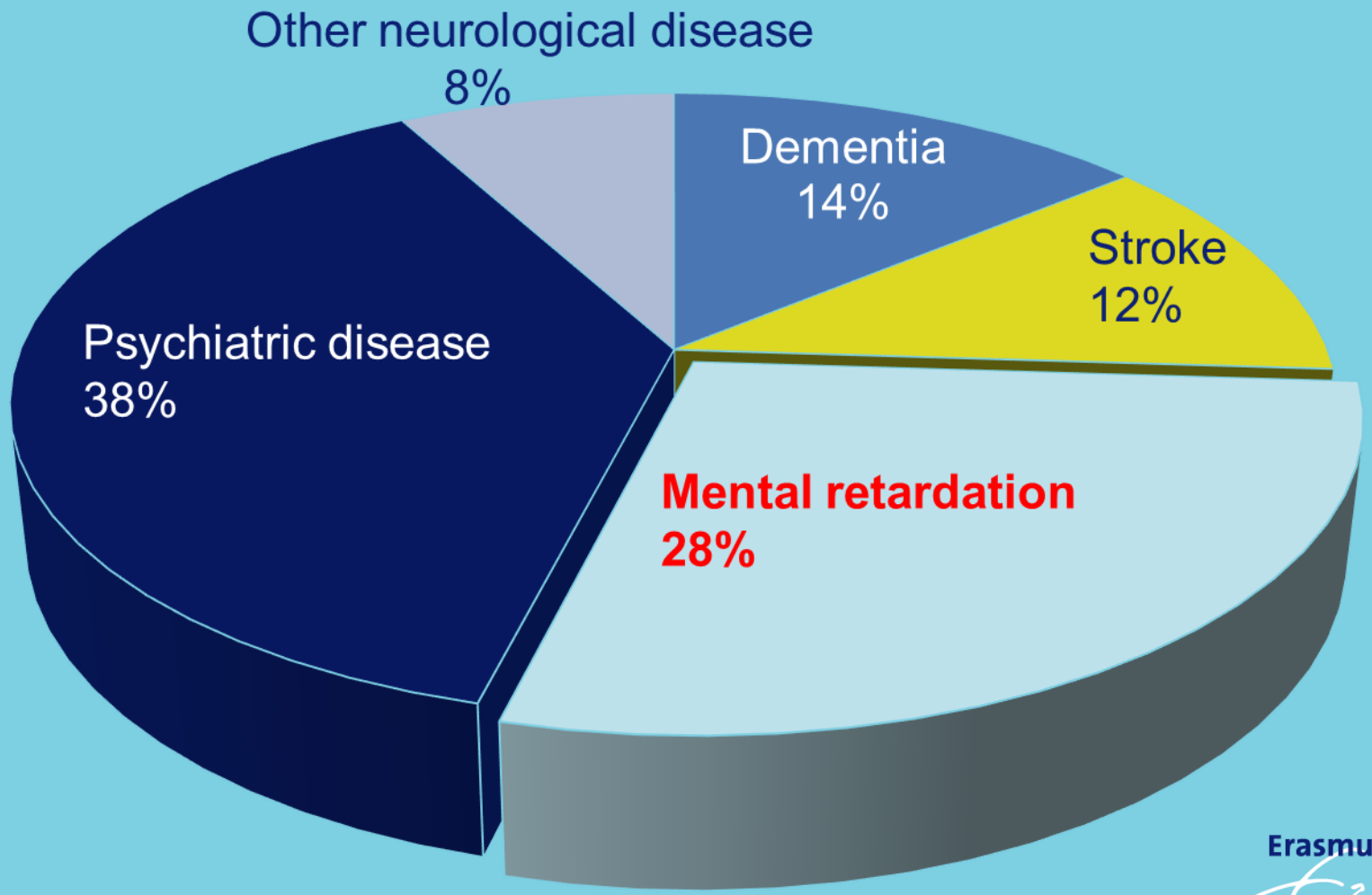
Costs to society of brain disease



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How to analyse a child with a developmental disorder

- Patient history: parents, social circumstances, daycare, school etc
- Physical examination
- Neurological examination

Use all your senses and basic tools to create a sensibel differential diagnosis

Than choose the most helpful technical evaluations

Important questions in patient history

- When was the developmental delay firts noticed?
- Slow development? No further development? Regression?
- Which aspects do not develop: mainly motor problem, language, behaviour?
- Family history? Relatives with similar problems? Consanguinity?
- Detailed history:

  Pregnancy, perinatal problems, developmental milestones, cerebral trauma, epilepsy,….

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Important is information on

-
  - ← visual, auditory sensory disturbances
  - ←Behaviour
  - ← Neglect / abuse
  - ←Intercurrent illness, environmental deprivation / hospitalisation
  - ←Familial occurence of similar developmental problems

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Focal neurological signs / symptoms

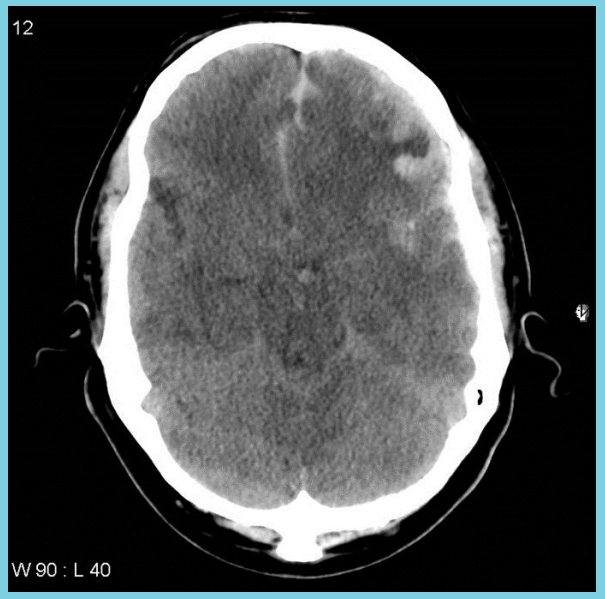
Mixed aphasia

Bradyphrenia

Behavioural disorder

Memory and concentration disorder

Right piramidal paresis



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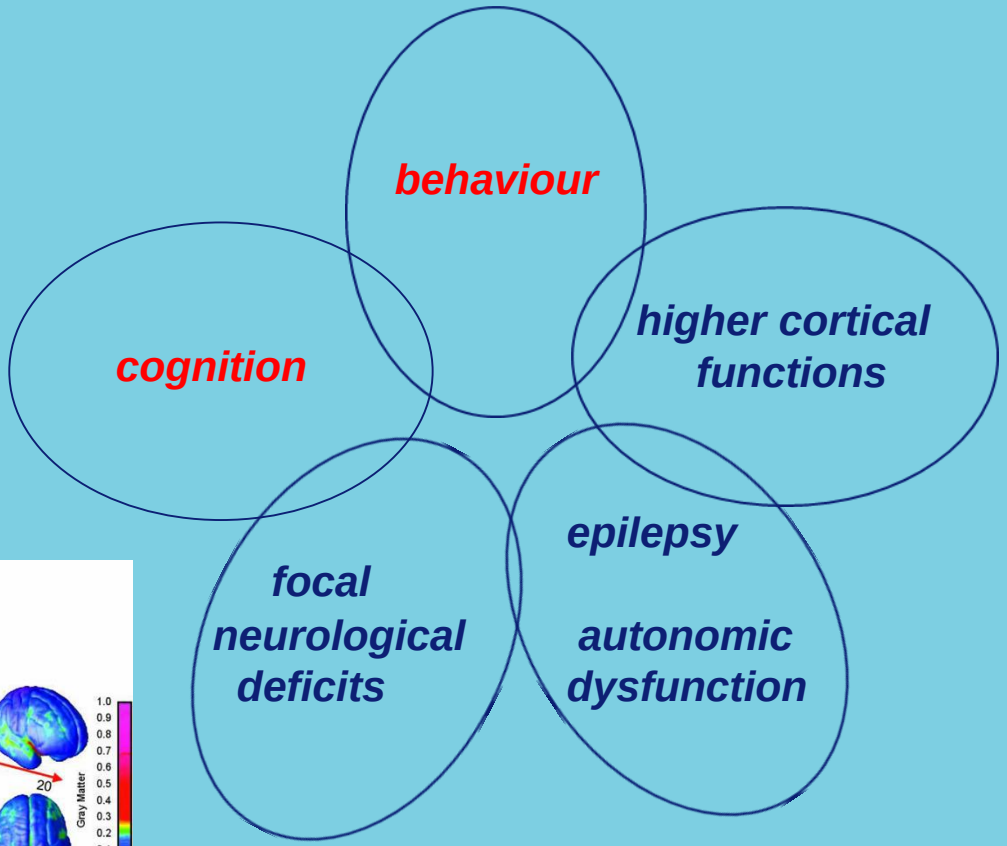
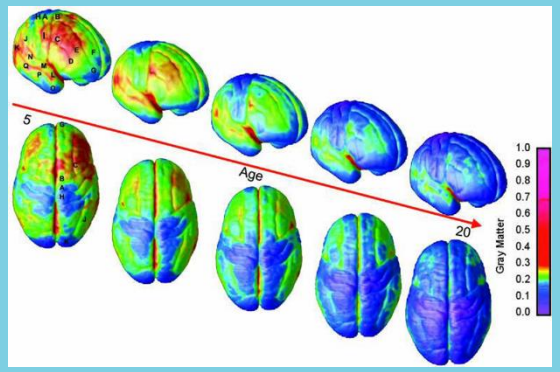
Disabilities after ABI may become apparent later in life through growing into deficit

- 50% of survivors of moderate-severe TBI have an unfavourable outcome
-





Cogtai et al 2004

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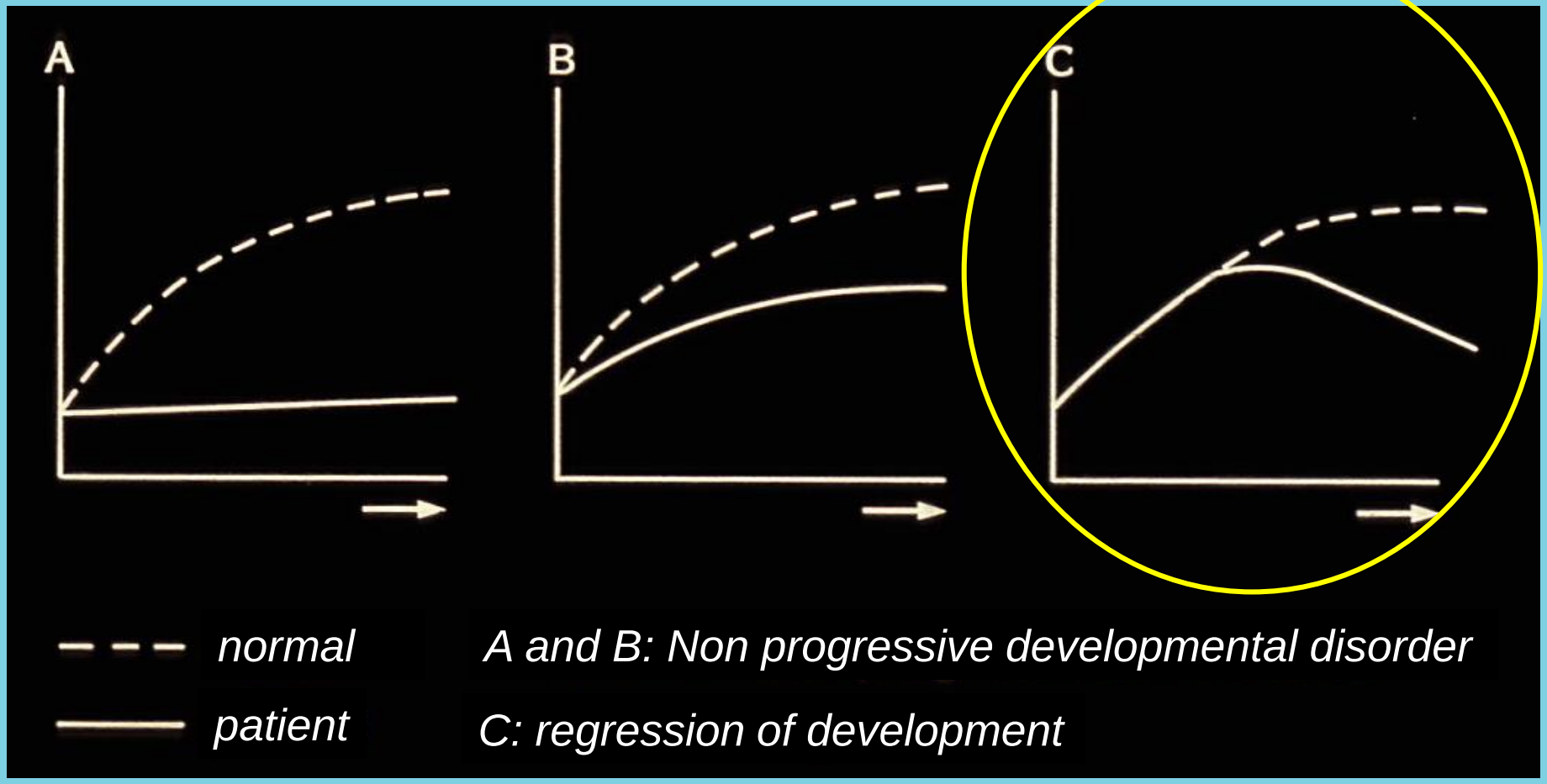
Decide the type of the developmental disorder



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Regression of development without obvious event

- **Common disorders**
- (Affective) abuse / neglect/
- Chronic illness (hospitalisation)
- Hypothyreoidie
- Intoxications (Pb)
- Deficiencies
- (low grade) brain tumour
- Chronic infections

- **Large group of rare diseases**

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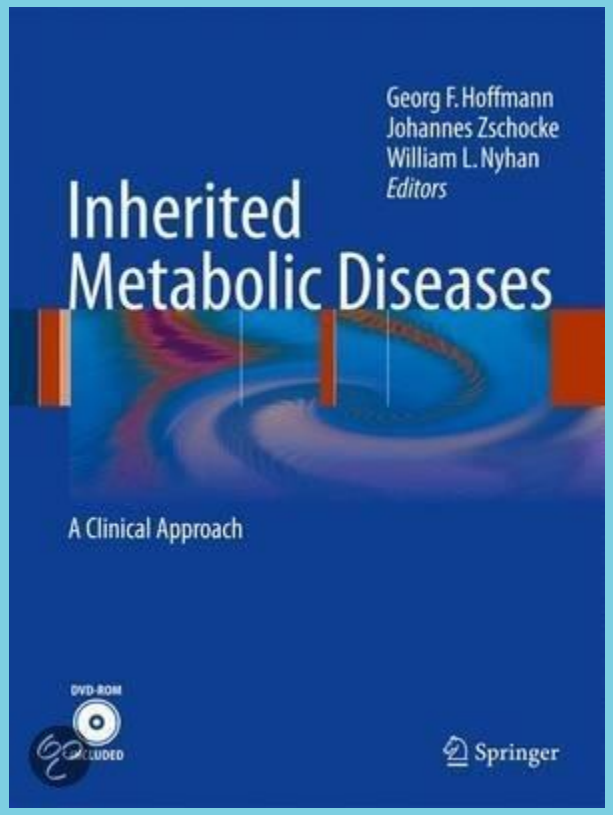
Rare diseases are a common cause of developental regression

- Metabolic diseases
  - Aminoacidopathies
  - Lysosomal diseases
  - Mitochondrial disease
  - Peroxisomal disease
  - Congenital defects of glycosylation (CDG)

- Many others
  - Rett syndrome
  - Limbic encefalitis
  - Infantile neuroaxonale dystrofy and related diseases
  - Etc ……..



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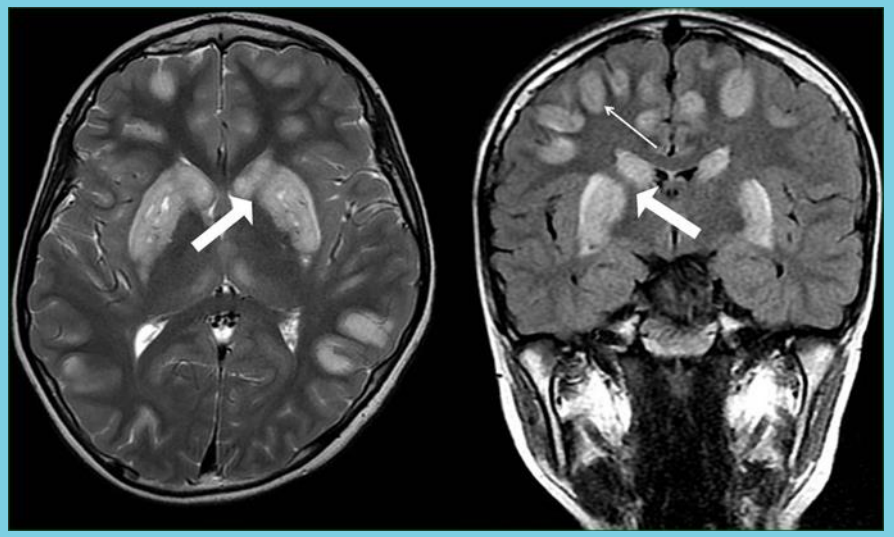
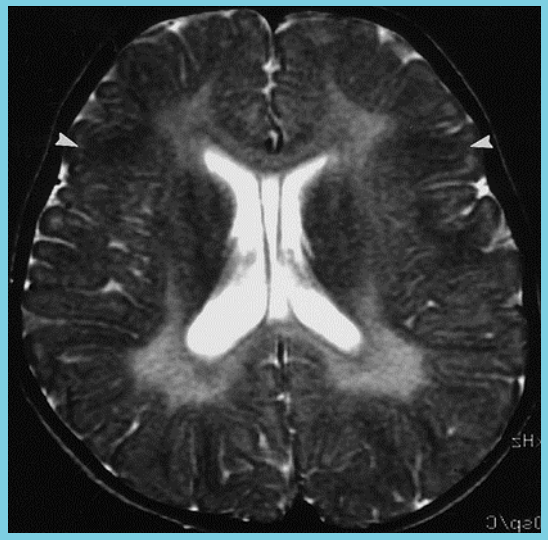
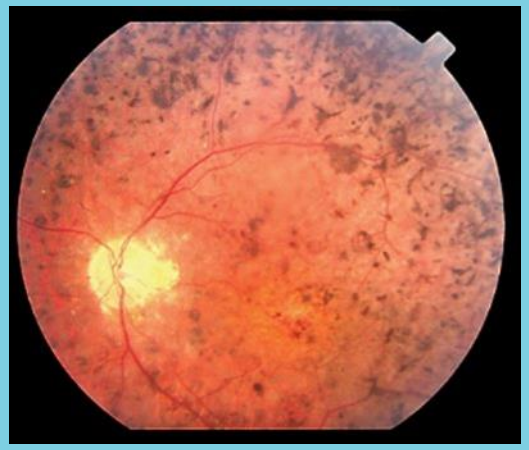
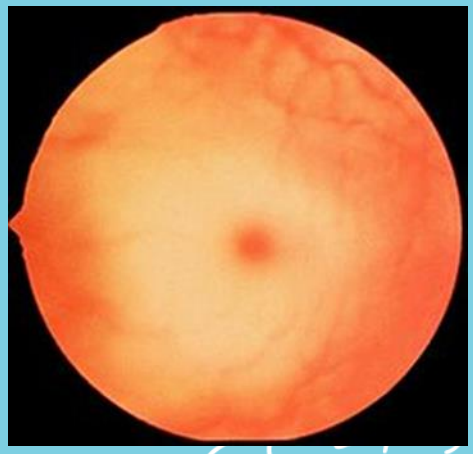
Analysis may be complicated and time consuming

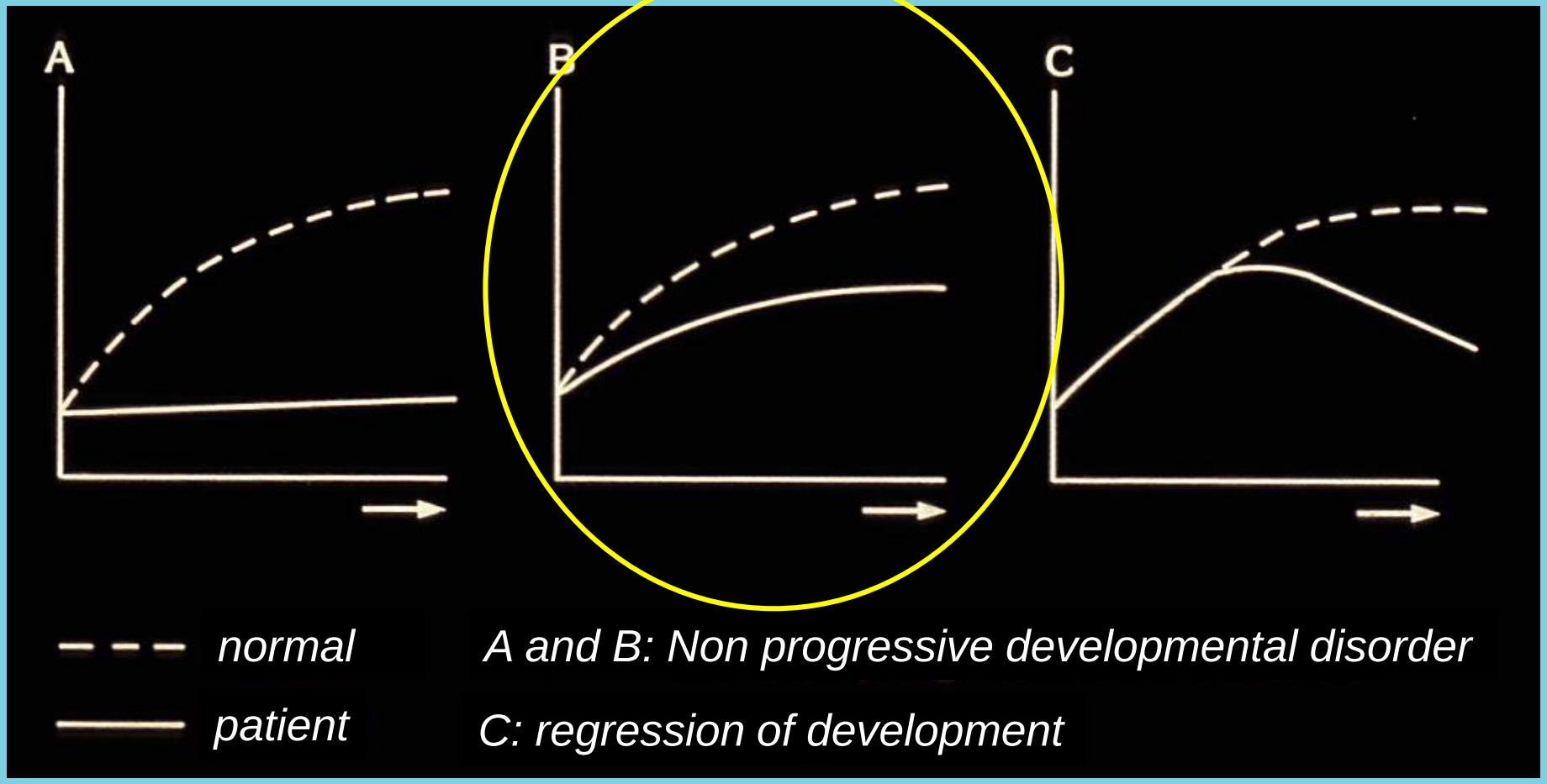








Decide the type of the developmental disorder



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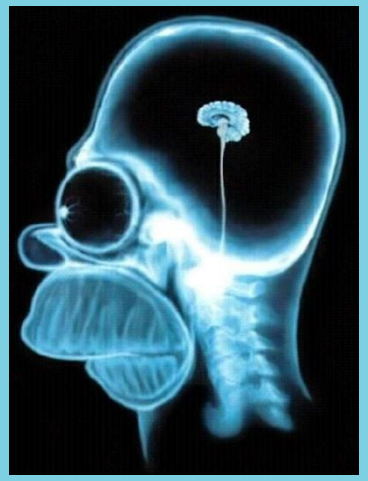
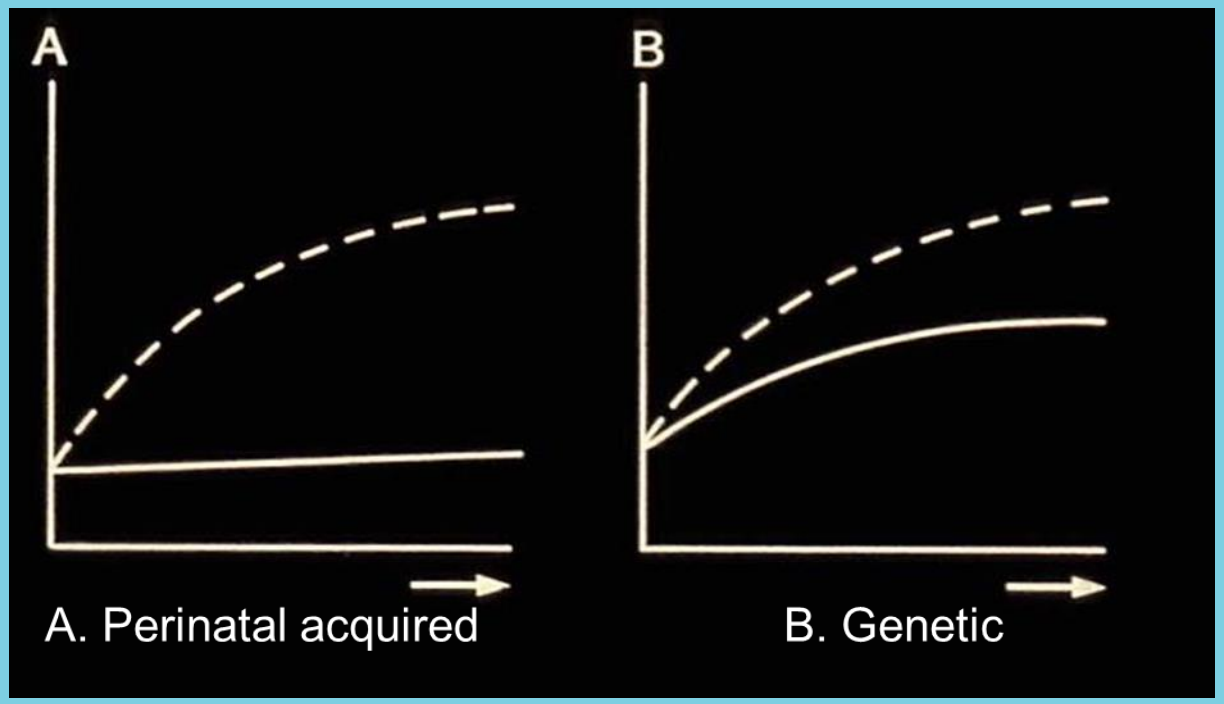
The red flags at first sight in children with developmental problems

- ← Skull circumference and shape
- ←Skin abnormalities
- ← locomotion
- ←Behaviour
- ←Dysmorfic features

Definition Microcephaly

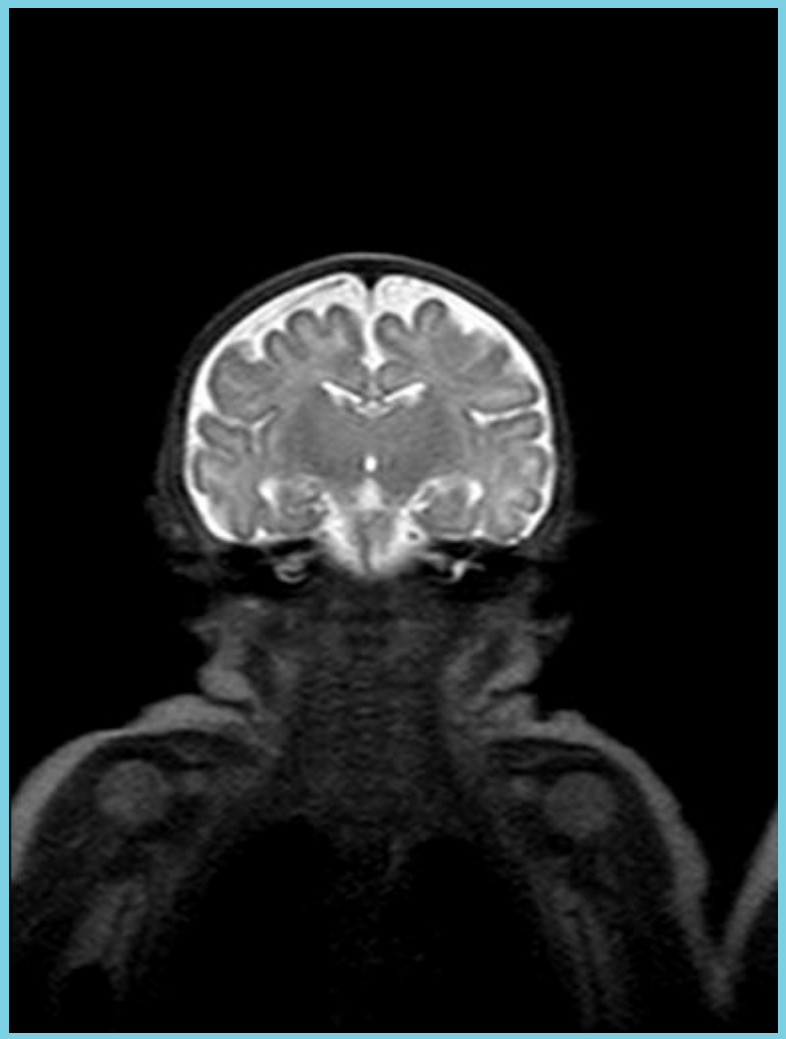
- Occipital-frontal circumference < -3 sd
  - Corrected for age, gender, gestation

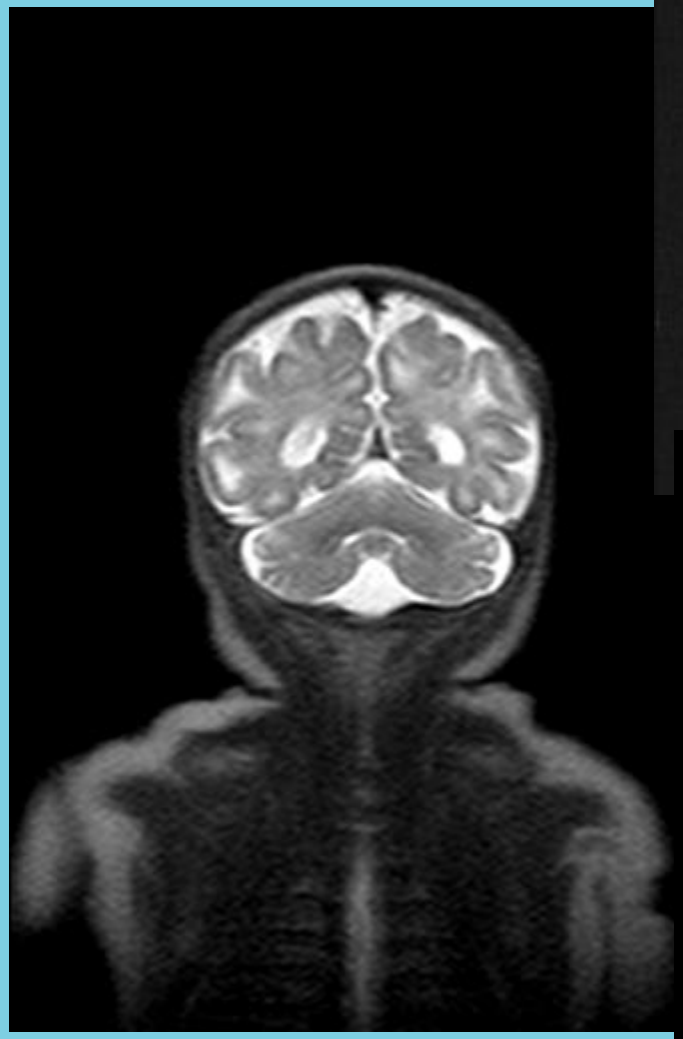


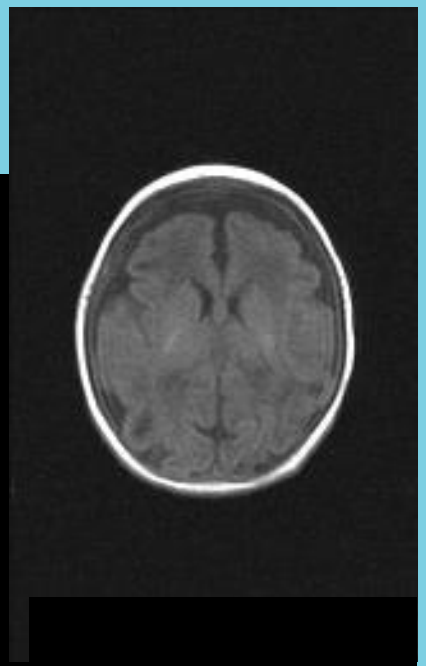


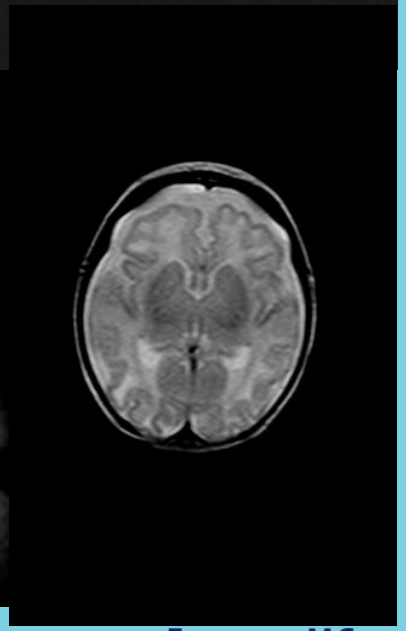
Growth pattern of different types of microcephaly

Describe what you see









Simplified gyral pattern

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Classification microcephaly

- Primary
  - Develops before 32th week of gestation
- Secondary
  - acquired

Etiological overlap between primary and secondary microcephaly

- Syndromal / genetic
- Metabolic disorder
- Environmental factors
- Infections

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Aetiology

acquired/ secondary micocephaly

- Traumatic
  - Infarction /hemorrhage
  - **(twin to twin transfusion)**
- Congenital Infection
  - TORCHES: Toxoplasma, Rubella, CMV, HSV, Syphilus: Zikka??
- *Deprivation (maternal)*
  - *Hypothyroidy*
  - *Malnutrition*
  - *etc.*
- Teratogenic (maternal)
  - Toxic: fetal alcohol syndrome, smoking, lead, pesticides, etc
  - Systemic disease (PKU, diabetes)
  - Medication (for example antiepileptic drugs)

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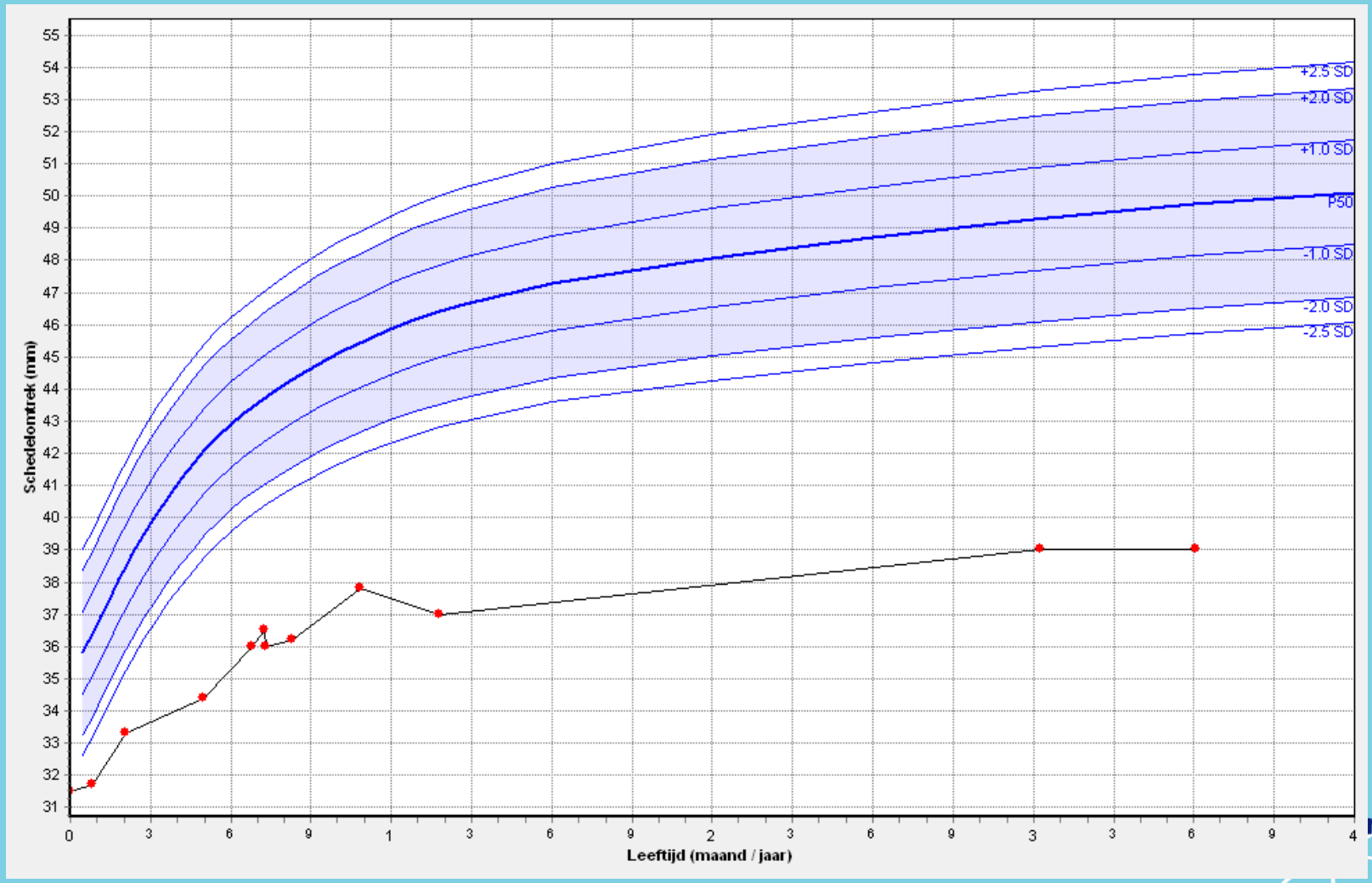
Diagnosis: Early Infantile Epileptic Encephalopathy type 10 (*PNKP-gen)*



Another example: Marilotte 2 ½ years old

- Developmental delay, SC < -3
  - Can crawl, sits unsteady, pulls to to standing
  - Does not speak, only grumbles
  - Situative understanding
  - Salivates a lot
  - Happy child, laughs a lot
  - Hyper-motoric behavior, waves with her hands
  - Loves playing with water

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Marilotte 2 ½ years old

- Ophtalmologist: no abnormalities .
- MRI brain: normal
- array: deletion chromosome 15:
- Angelman syndrom or PWS ?
- DNA : Angelman syndrome

http://www.youtube.com/watch?v=bzVZ8QLQH2w

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DIAGNOSTIC CRITERIA (2005)

- ***A. Consistent features (100%)***
  - 1. **Developmental delay, functionally severe**.(IQ 20-30)
  - 2. **Movement or balance disorder**, usually ataxia of gait, and**/**or tremulous movement of the limbs. Movement disorder can be mild. May not seem as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions.
  - 3. **Behavioural uniqueness**: any combination of frequent laughter**/**smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping movements, or waving movements; hypermotoric behaviour.
  - 4. **Speech impairment**, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones.
- ***B. Frequent features (more than 80%)***
  - 1. **Delayed, disproportionate growth in head circumference**, usually resulting in microcephaly (<_2 SD of normal OFC) by age 2 years. Microcephaly is more pronounced in those with 15q11.2-q13 deletions.
  - 2. **Seizures**, onset usually <3 years of age. Seizure severity usually decreases with age but the seizure disorder lasts throughout adulthood.
  - 3. **Abnormal EEG**, with a characteristic pattern of large amplitude slow-spike waves. The EEG abnormalities can occur in the first 2 years of life and can precede clinical features, and are often not correlated to clinical seizure events.

Dysmorfic features

- Light skinned, blond hair
- Facial features become more prominent in time
- brachy-microcephaly
- broad face, narrow mid-face
- broad mouth, wide spaces between teeth
- Pointed chin, later mandibulare prognathy
- Tongue protrusion

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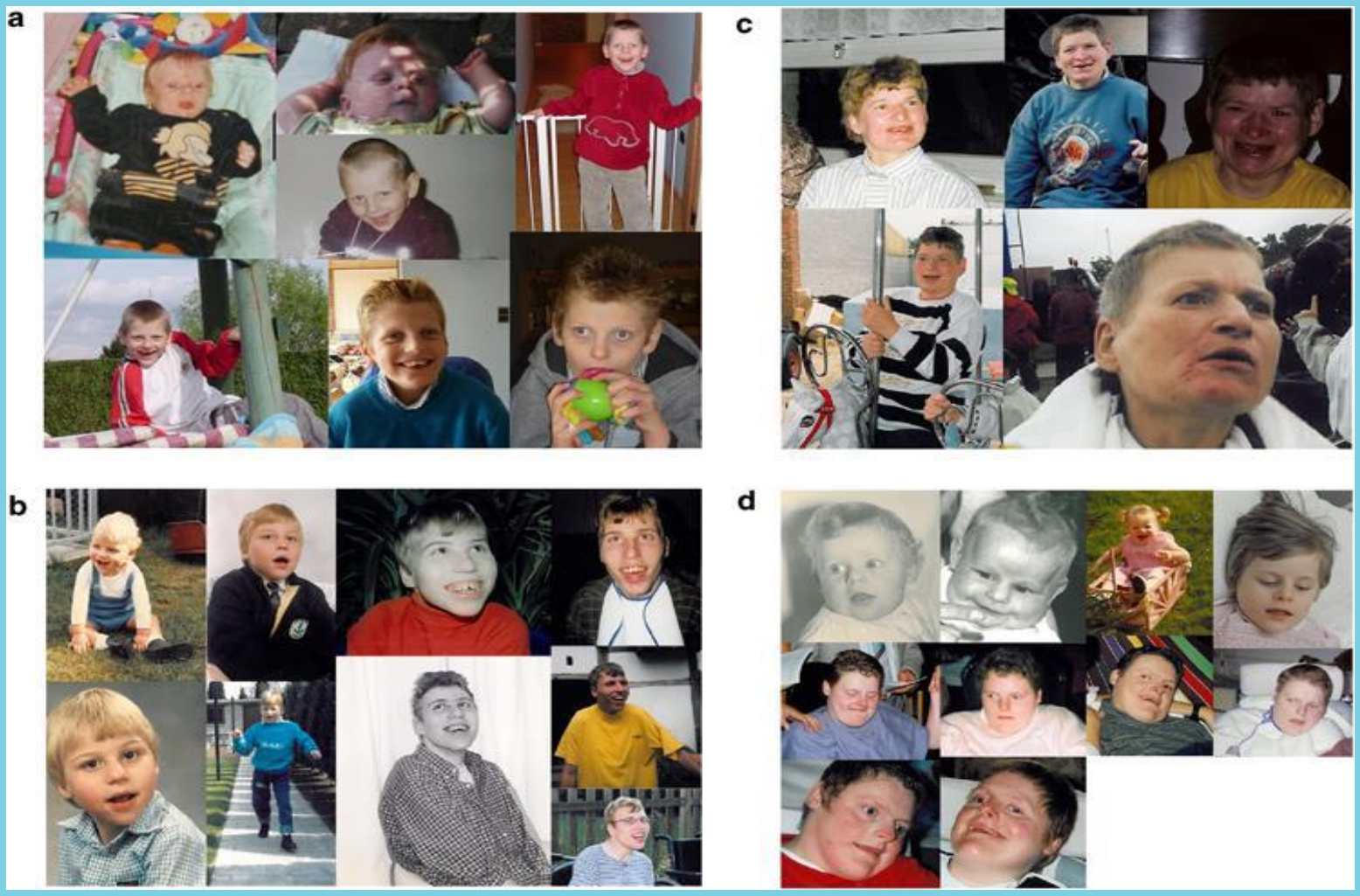
Dysmorphic features in Angelman syndrome become more evident later in life



Van Buggenhout et al, Eur J Hum Genet 2009;17:1367-1373

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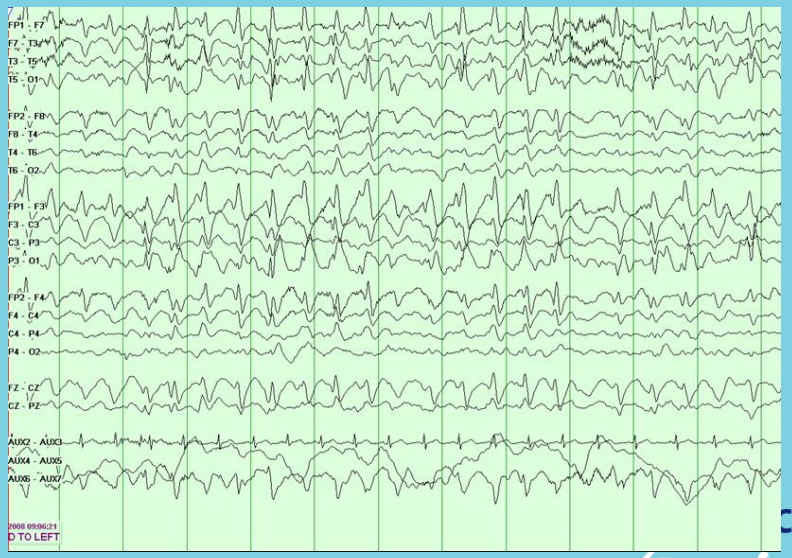
Epilepsy in Angelman syndrom

- 85 % epilepsie
- onset at age 12-18 months
- No specific type of epilepsy
- May hav very long lastig (weeks) partiel status
- EEG, with a characteristic pattern of large amplitude slow-spike waves
- Often refractory



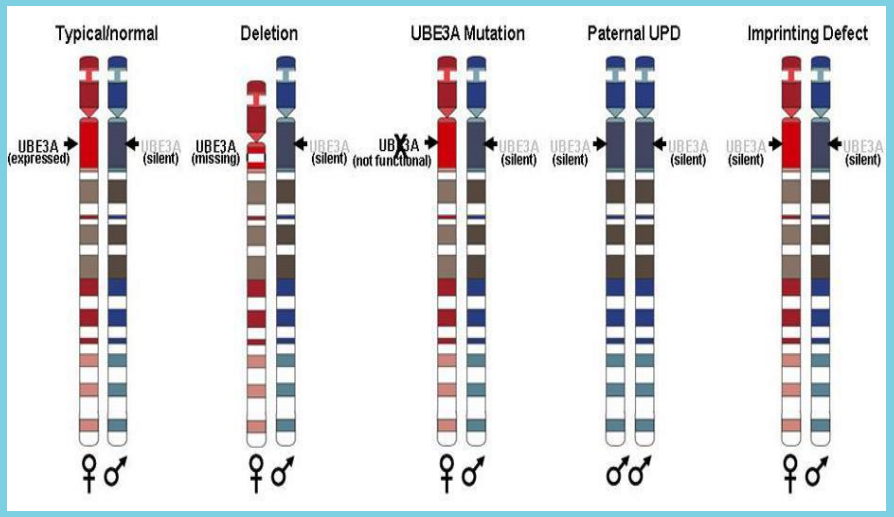
Behavioural characteristics

- hand-flapping (happy puppet)
- social smiling without babbling, later typcal bout of laughter
- Social children
- Hyperactive, impulsive, easily distracted
- Fixations (specific food, water)
- Autistiform behavioural features
- Sterotype movements
- Later rigidity

- http://youtu.be/lpWl2DucZM4

Genetics

- central role UBE3A gene on *maternal* chromosome 15q11-13
- in 90% genetic diagnosis possible
- Almost always de novo mutation
- 4 variants
  - 1. deletion 15q11-13 (70%)
  - unipaternal disomy (3%)
  - imprinting deficit (5%)
  - UBE3A-mutation (20%)



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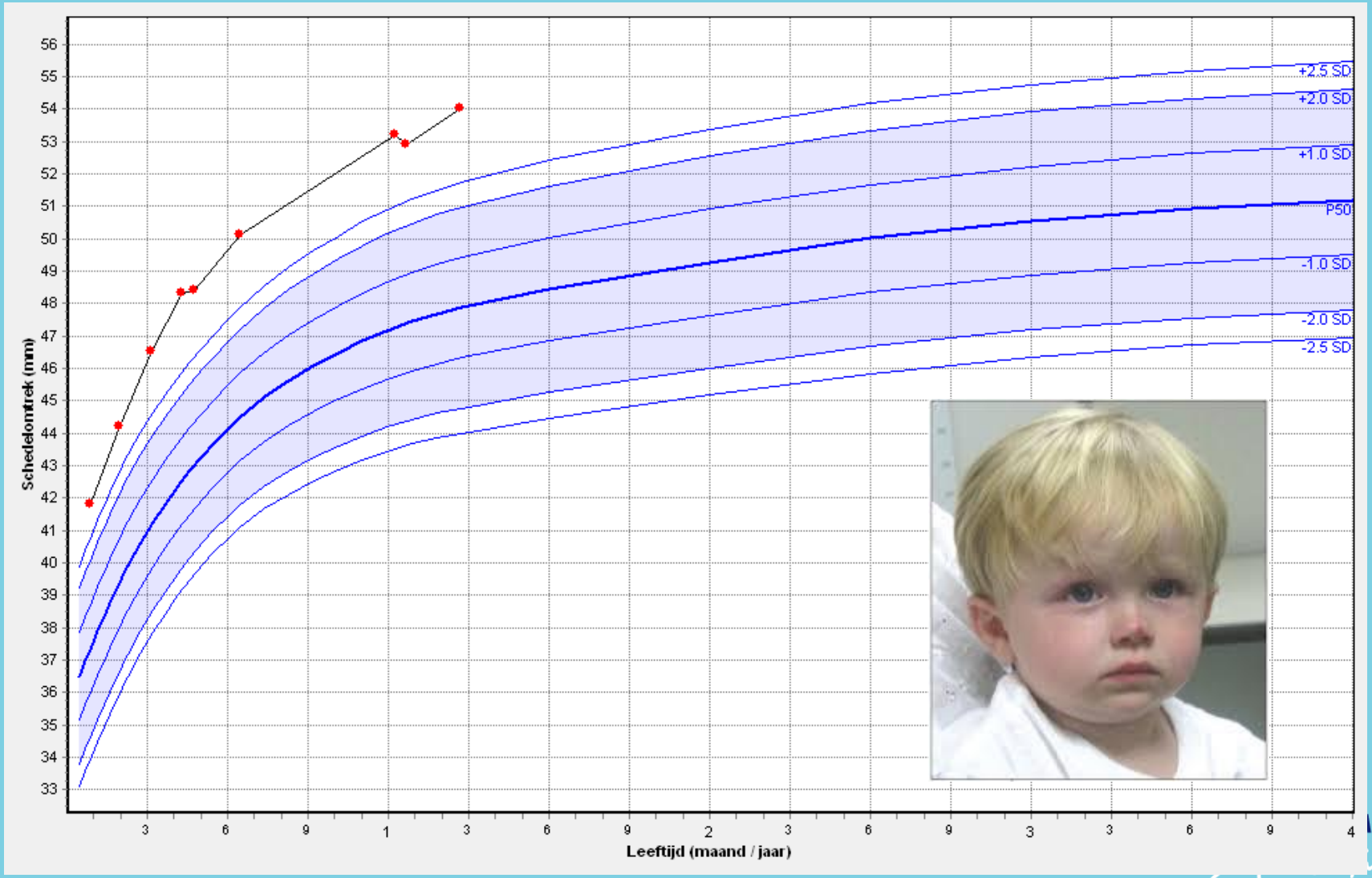
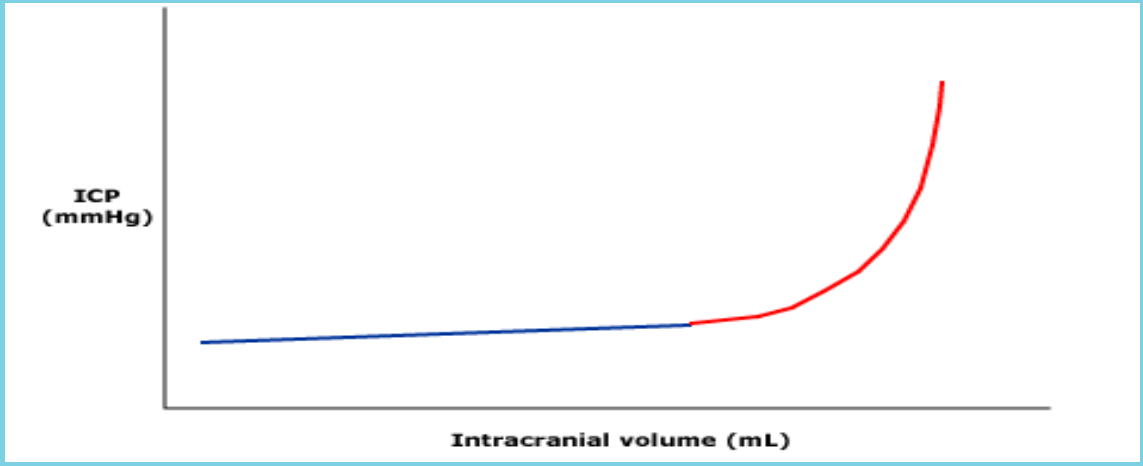
Skull circumference >3SD: Macrocephaly



Etiology

- Abnormal increase of one of the components in the skull :
  - Spinal fluid
  - Blood
  - Bone
  - Brain tissue



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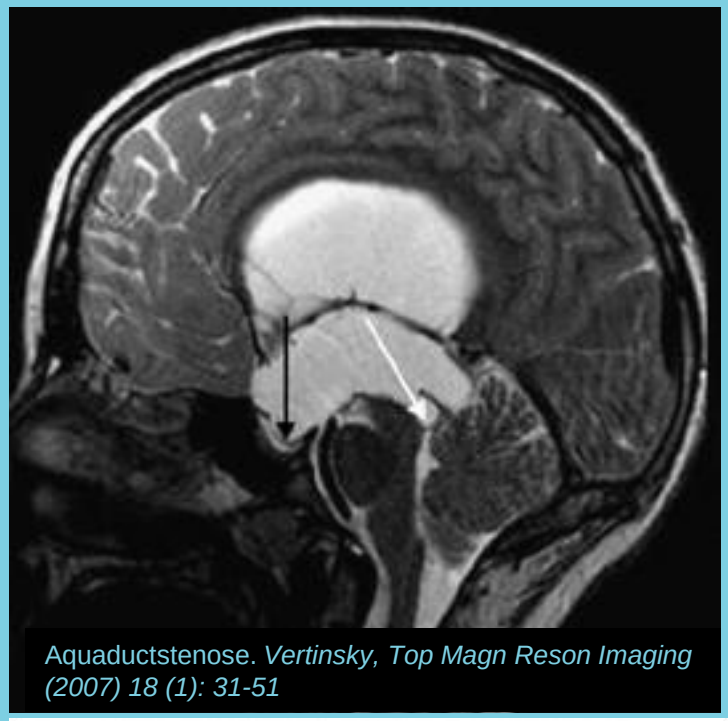
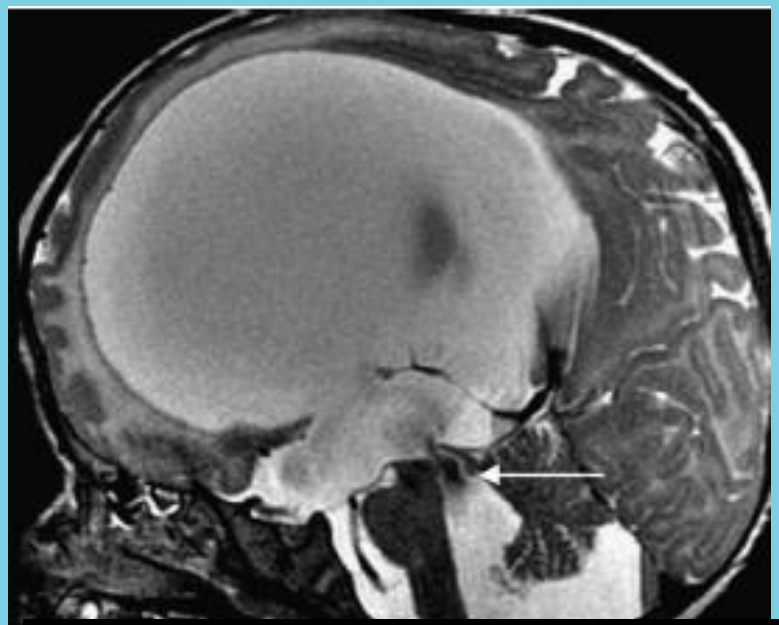
Increase spinal fluid volume

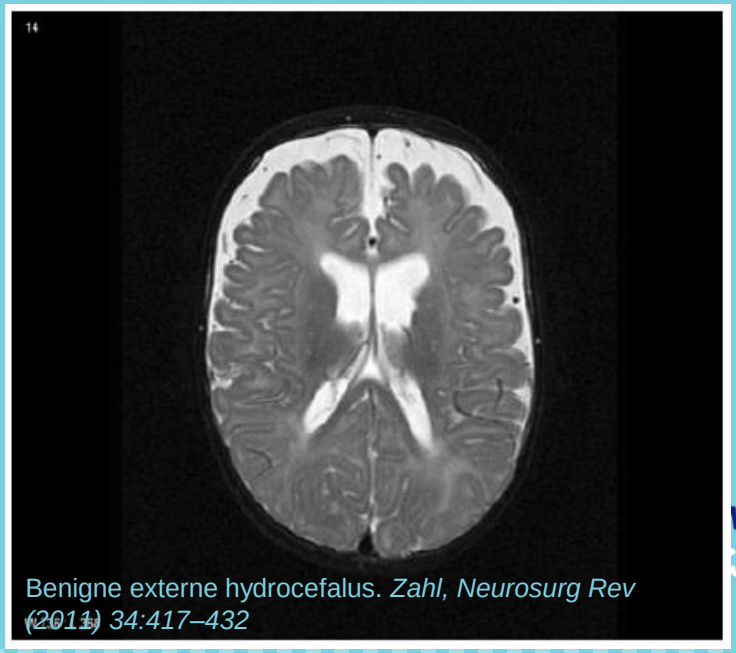
- Communicating hydrocephalus
- Obstructive hydrocephalus
  - Primary
  - Secundary
- Benign external hydrocephalus



Aquaductstenose. *Vertinsky, Top Magn Reson Imaging (2007) 18 (1): 31-51*



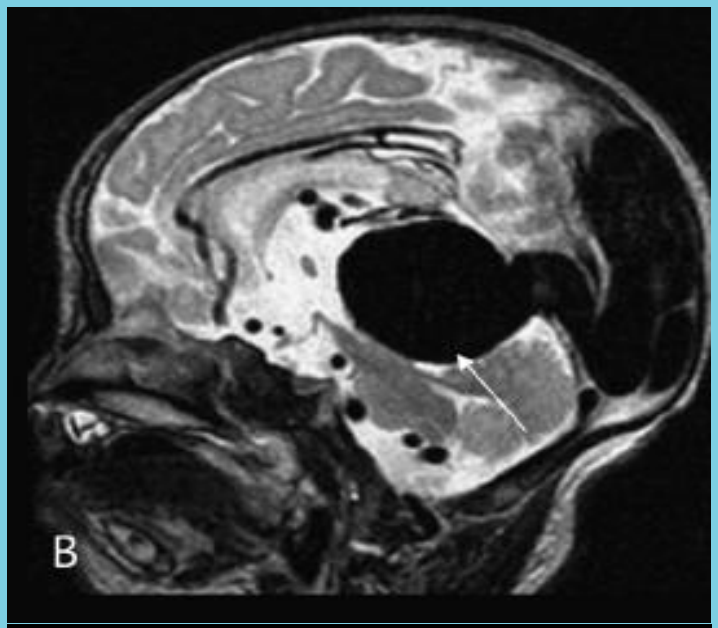
Posthemorrhagische comm hydrocefalus. *Vertinsky, Top Magn Reson Imaging (2007) 18 (1): 31-51*



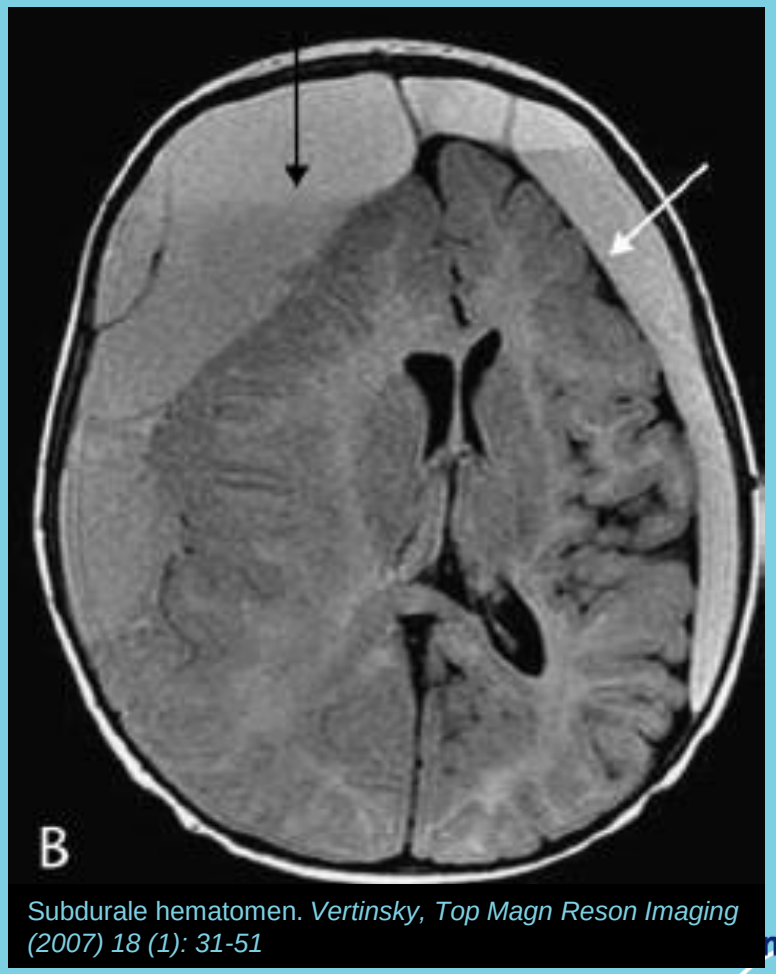
Benigne externe hydrocefalus. *Zahl, Neurosurg Rev (2011) 34:417–432*

Increased volume blood in other compartments

- (Chronic) subdural hematoma
- Hygroma
- Empyema
- Vein of Galen malformation



Vene van Galen malformatie. *Vertinsky, Top Magn Reson Imaging (2007) 18 (1): 31-51*



Subdurale hematomen. *Vertinsky, Top Magn Reson Imaging (2007) 18 (1): 31-51*

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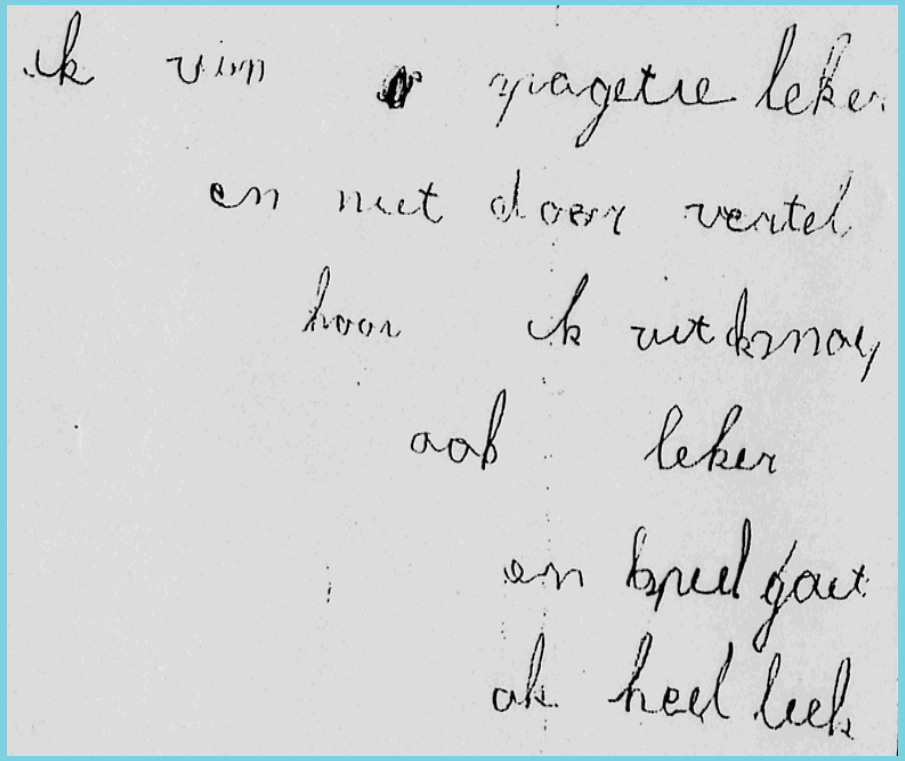
8 years old girl: SC > 3 SD

- School results deteriorated during the past year
- Calculation A → D
- Handwriting is harder to read
- becomes more clumsy
- slow
- no other symptoms/ complaints



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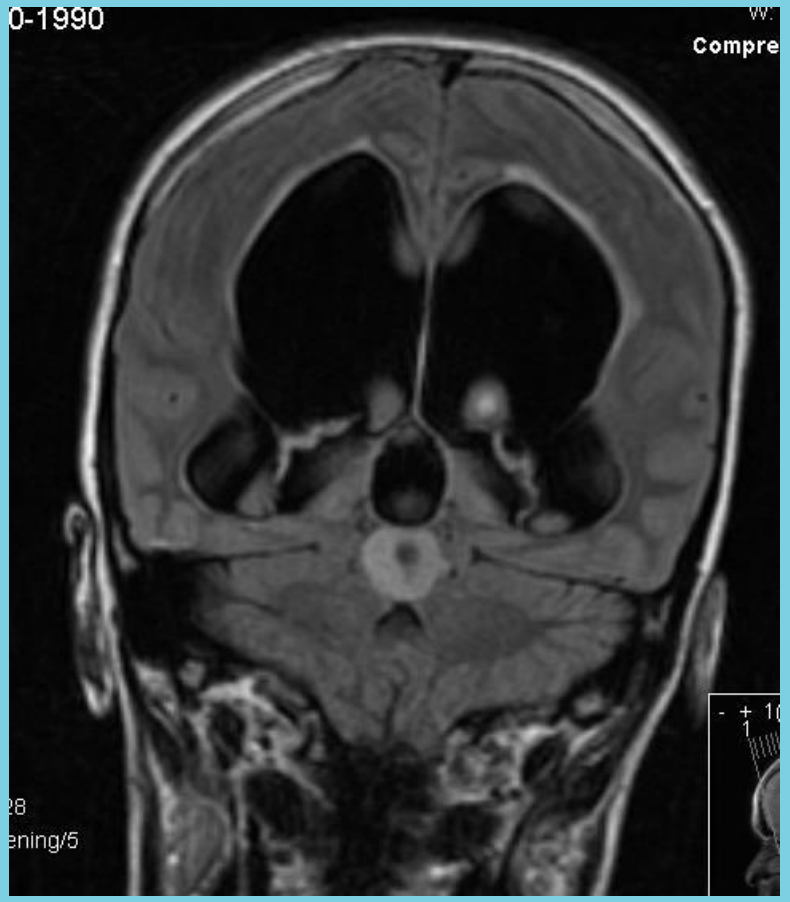

- MRI: obstructive hydrocephalus associated with a small tumor in the mesencephalon

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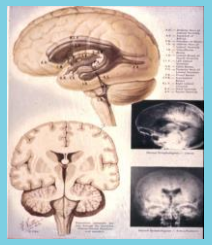
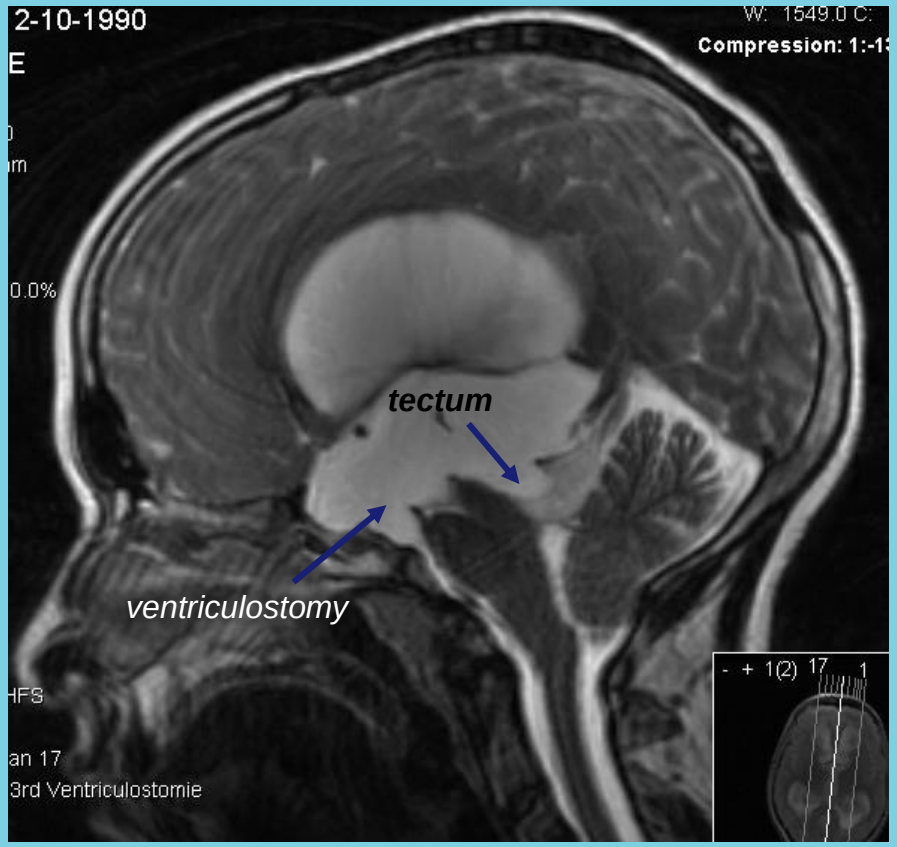
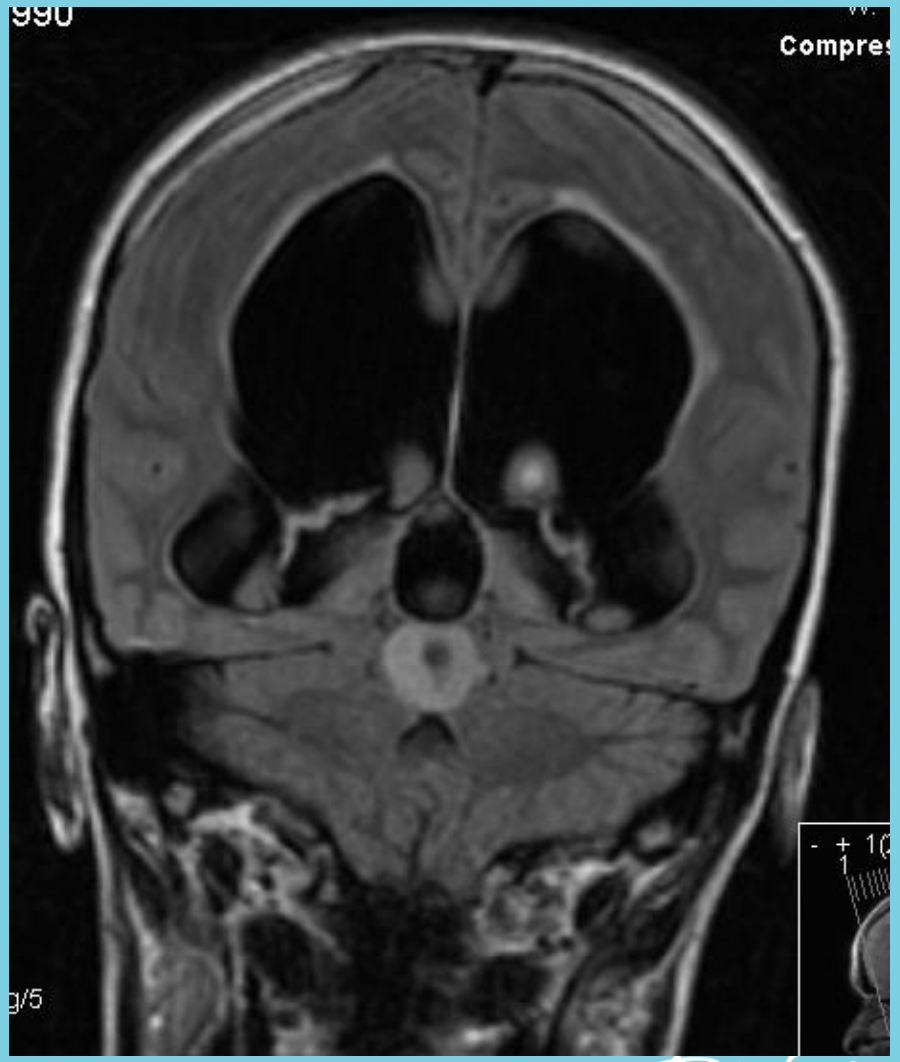
Obstructive hydrocephalus in a girl with a tectum glioma

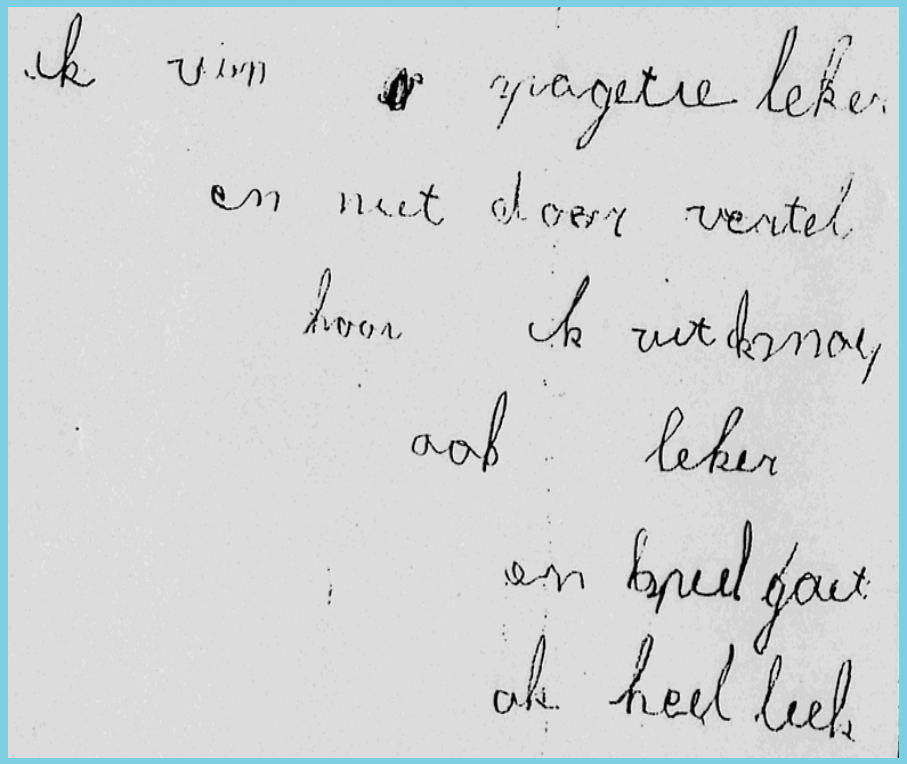




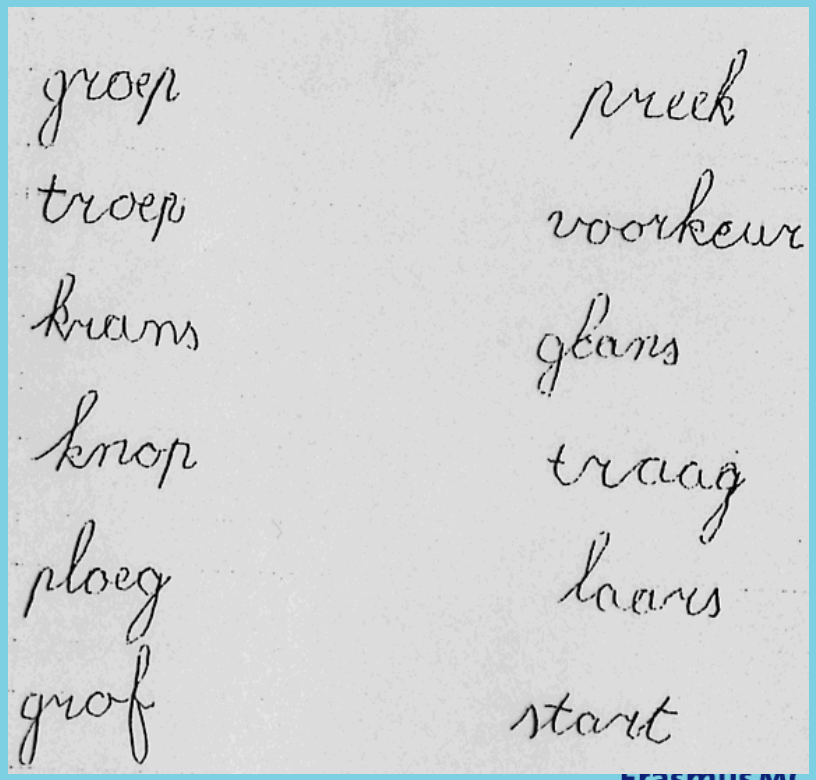


Treatment: ventriculostomy

- Neglect/ inattention before ventriculostomy



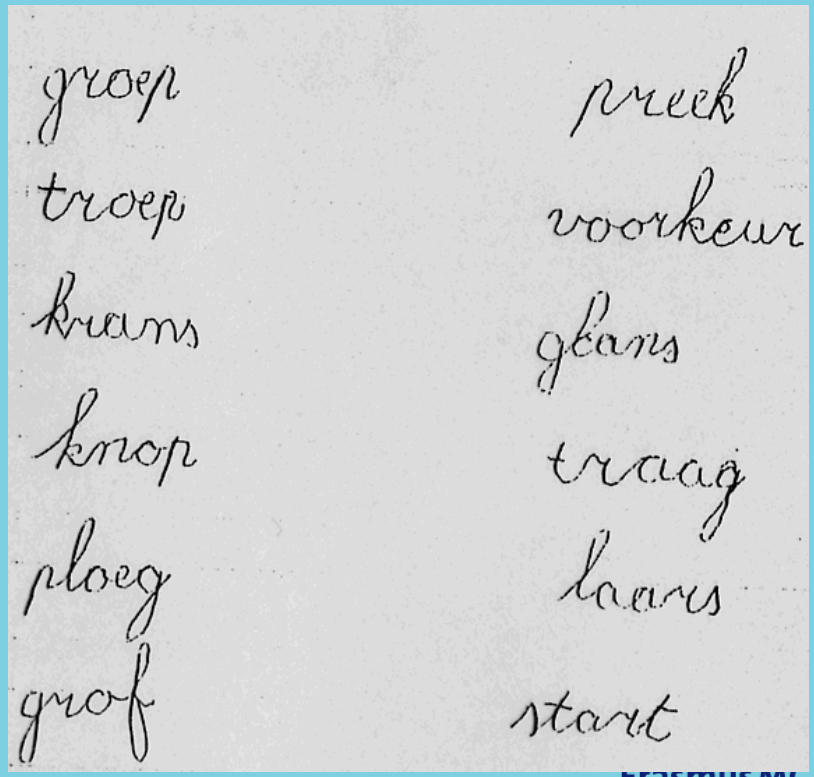
- Neglect/ inattentie after ventriculostomy



Treatment: ventriculostomie (tumor stabiel)

- **Follow up:**
- Finished high school
- Now in college
- No motor problems
- No endocrine problems

- Neglect/ inattention after ventriculostomy



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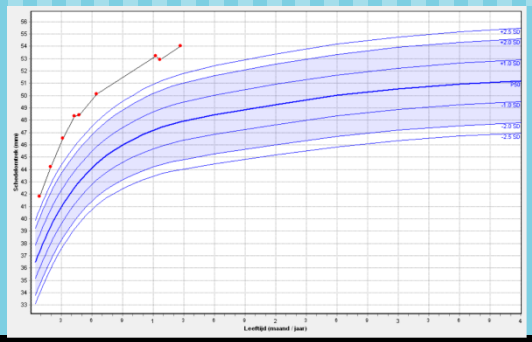
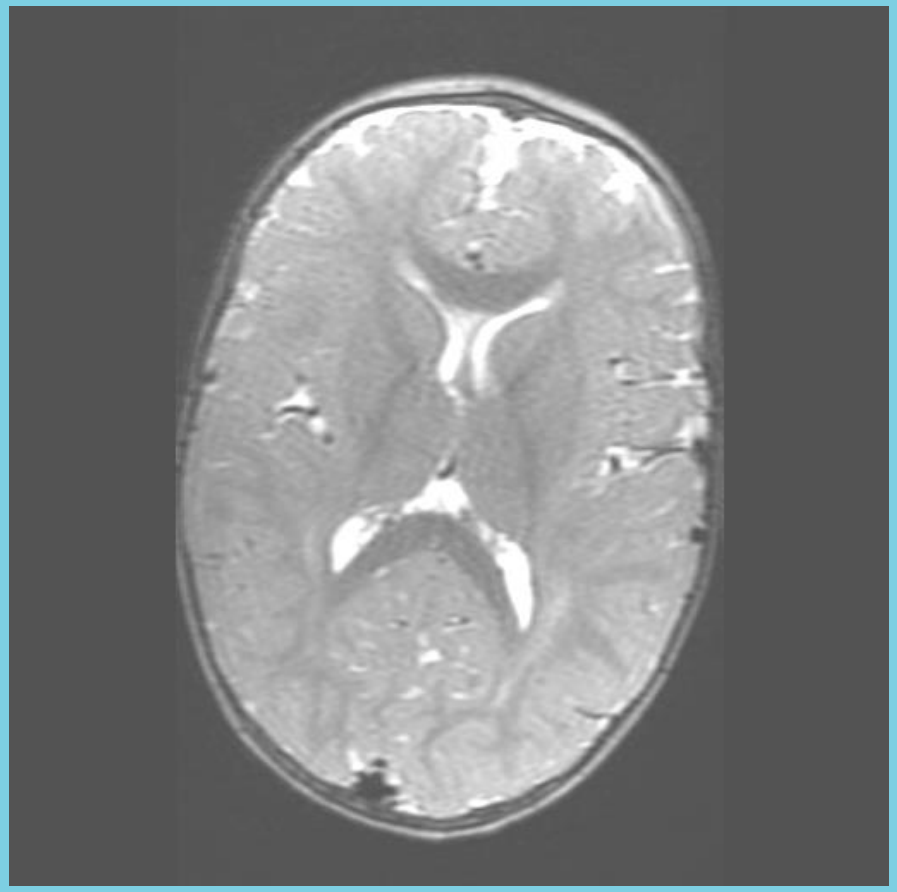
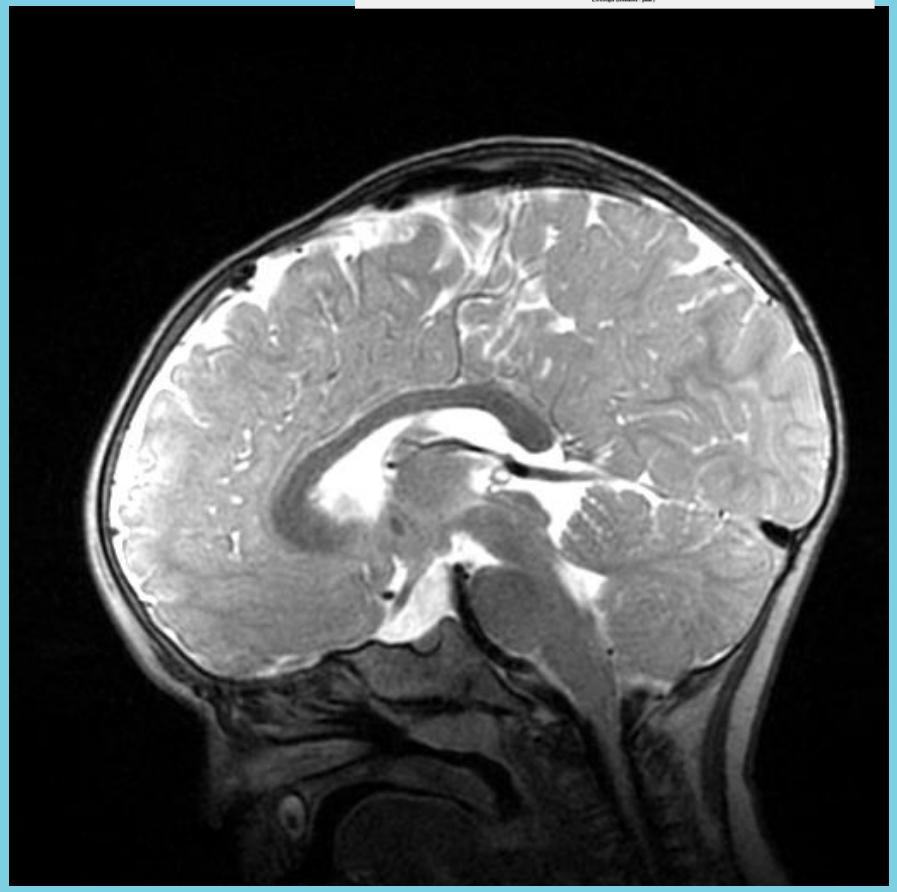
Increased growth of brain

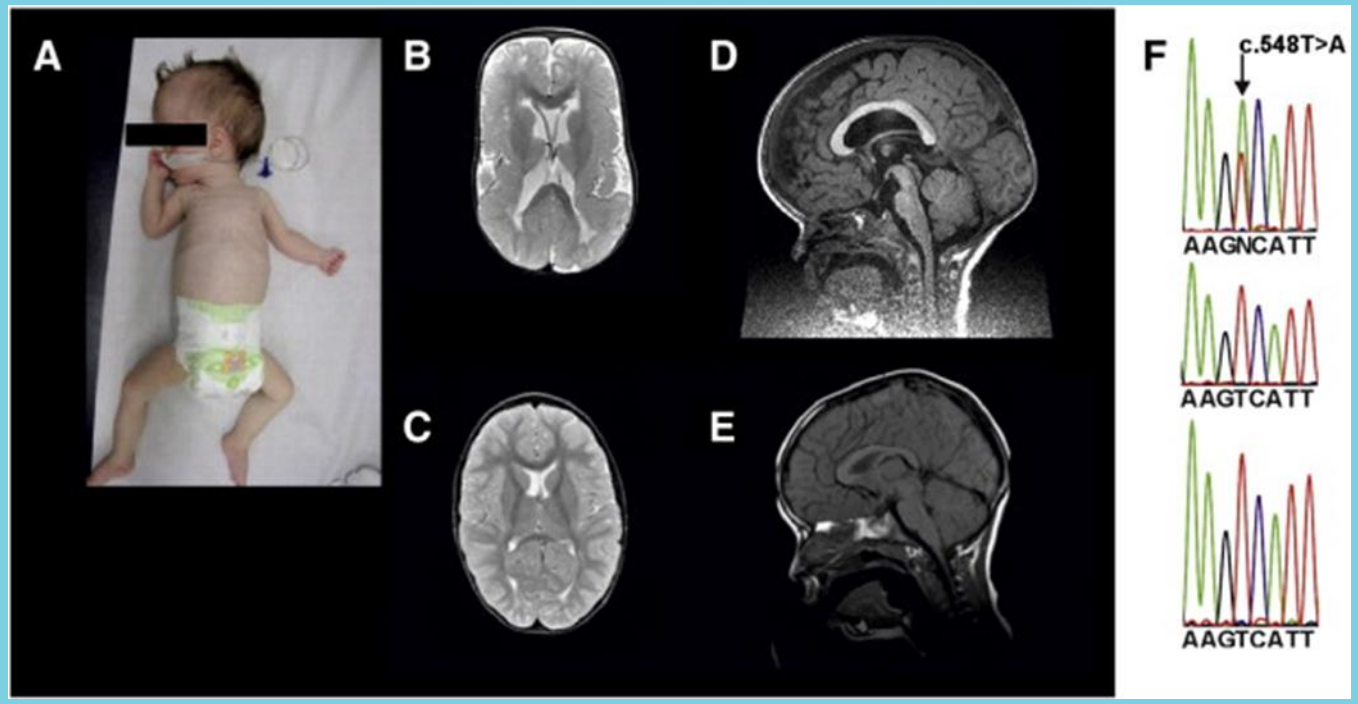






Erasmus MC

AKT 3 mutation: megalencephaly and mental retardation



Nellist et al: Germline activating AKT3 mutation associated with megalencephaly, polymicrogyria, epilepsy and hypoglycemia. Molecular Genetics and Metabolism 114;3: 2015, 467–73

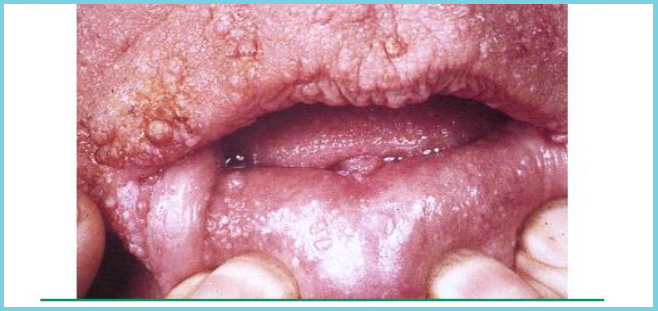
Erasmus MC

Increased growth of brain tissue

- **Metabolic disease**
  - Mucopolysaccharidosis
  - Mucolipidosis

Increased growth of brain tissue

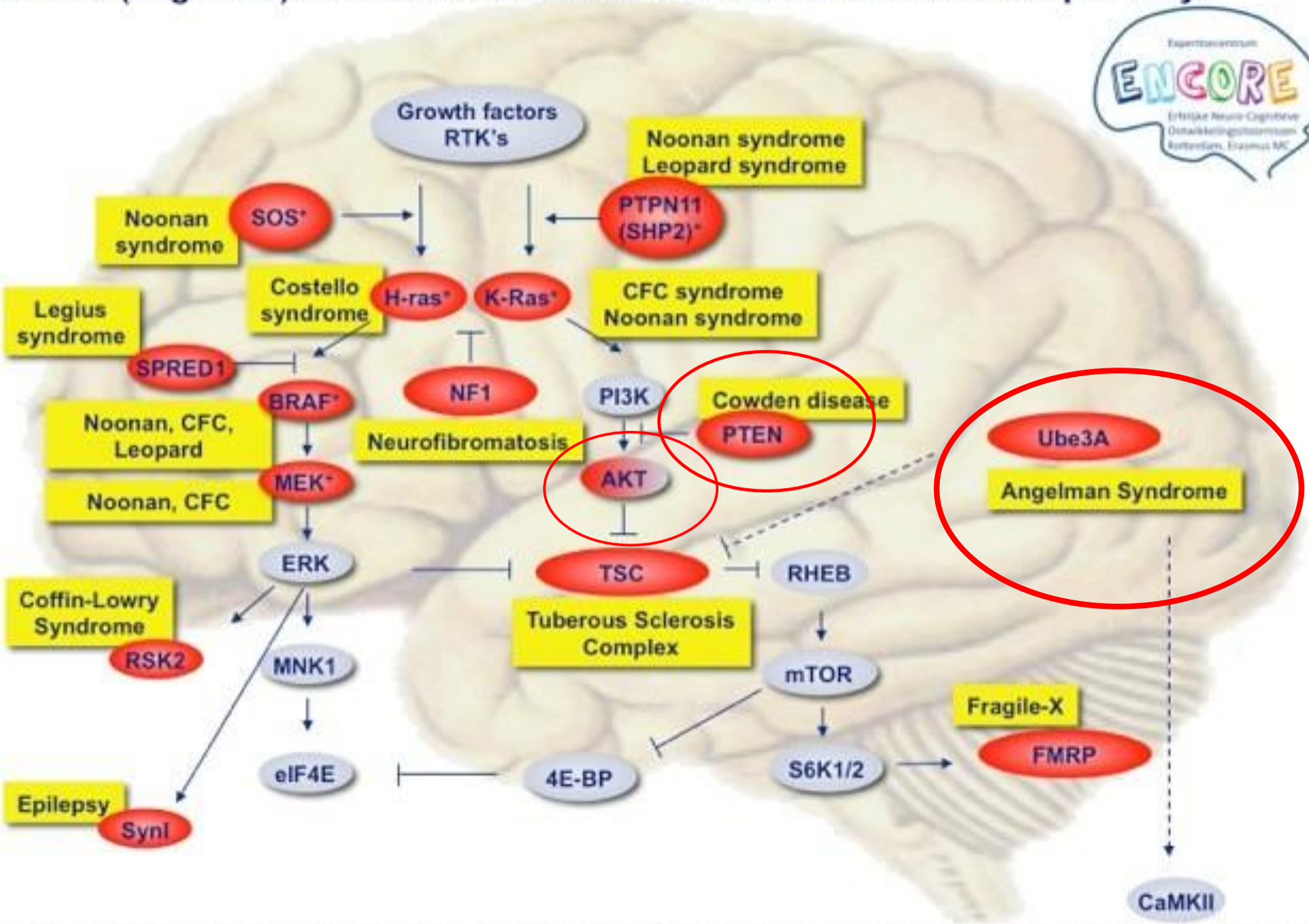
- Normal neurological investigation
  - overgrowth,
  - *PTEN* hamartoma, mental retardation
  - Neurocutaneous syndromes



***Cowden**: Orale papilloma and trichilemmoma*

Erasmus MC

Genetic (cognitive) disorders associated with the RAS/ERK/mTOR pathway



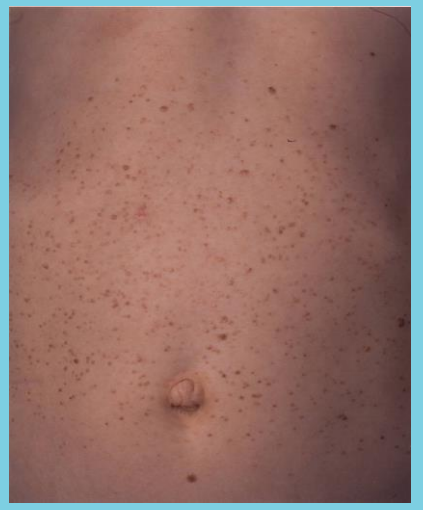
Basal cel naevus syndrome / Gorlin syndrome : chromsome 9q 22-23 –PTCH1 gen

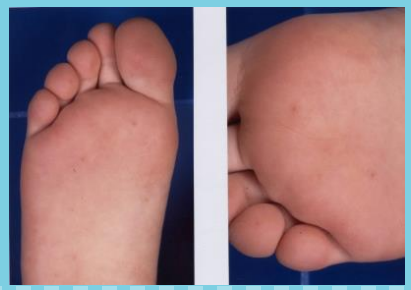
- Learning problems

- Dysmorfisms:

  Macrocephaly, hypertelorism

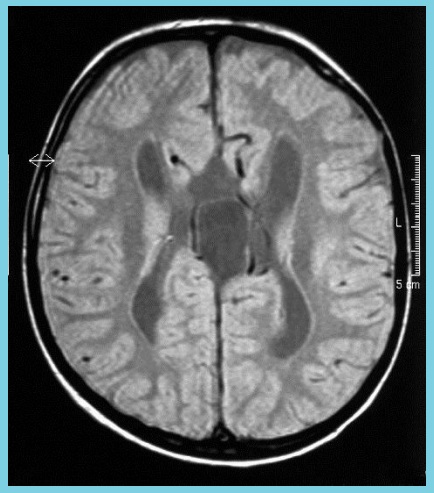
- Skin
  - Basal cel carcinomas on sun exposed skin
  - Palmar pits op voetzolen en handen
- Skelet deformities
  - Odontogenic cysts of the jaw, spina bifida occulta, kyfoscoliosis, rib abnormalities

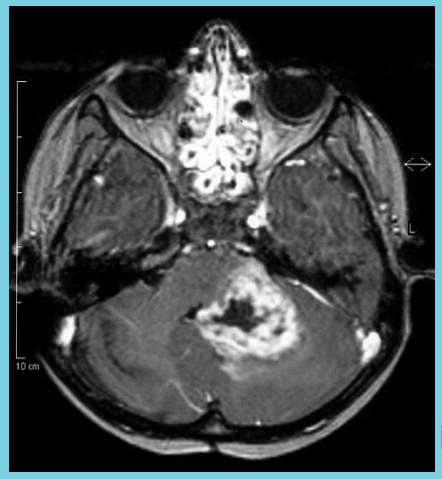




Basal cel naevus syndrome / Gorlin syndrome : chromosome 9q 22-23 –PTCH1 gen

- **CNS**
  - Hydrocephalus.
  - Agenesis Corpus Callosum
  - Medulloblastoma (5%)



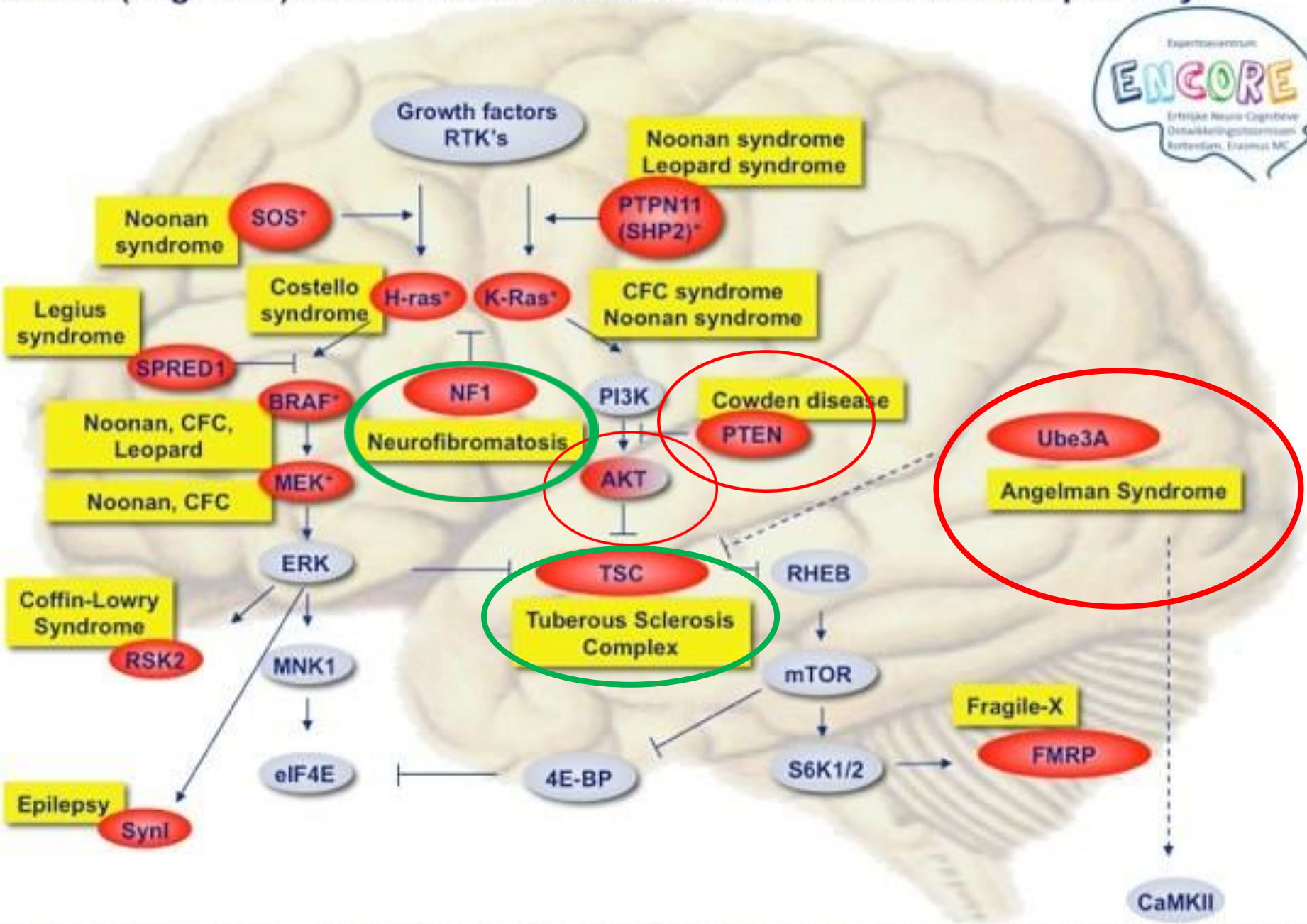


Erasmus MC

Macrocephaly AND skin abnormalities in children with a developmental and behavioural disorder

-

Genetic (cognitive) disorders associated with the RAS/ERK/mTOR pathway



Macrocephaly AND skin abnormalities in children with a developmental and behavioural disorder

- Neurofibromatosis

- Two or more of the following clinical features must be present:

  - Summary of NIH diagnostic clinical criteria for NF1

    the first step for us clinicians!

Erasmus MC

NF1: summary of general characteristics

- **NF1 is a multisystem disease and not rare !!**

- Incidence: approximately 1 in 3000 individuals

- - Mutations in the *NF1* gene, located at chromosome 17q11.2 -
- - many pathogenic mutations recognised
- - poor genotype- fenotype correlation

- Neurofibromin is the protein product encoded by the gene

- Neurofibromin is expressed in many tissues, including brain, kidney, spleen, and thymus, osteocytes

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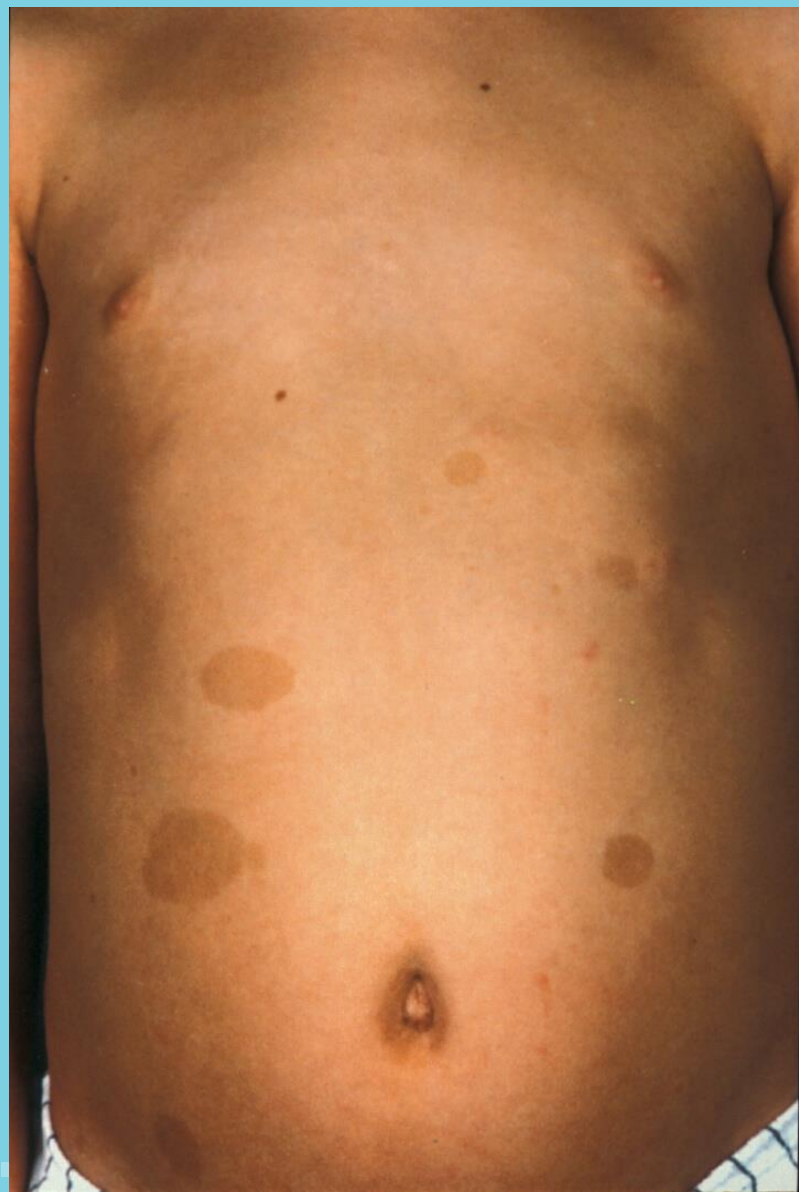
Clinical diagnostic criteria NF1

1. Six or more café au lait maculae

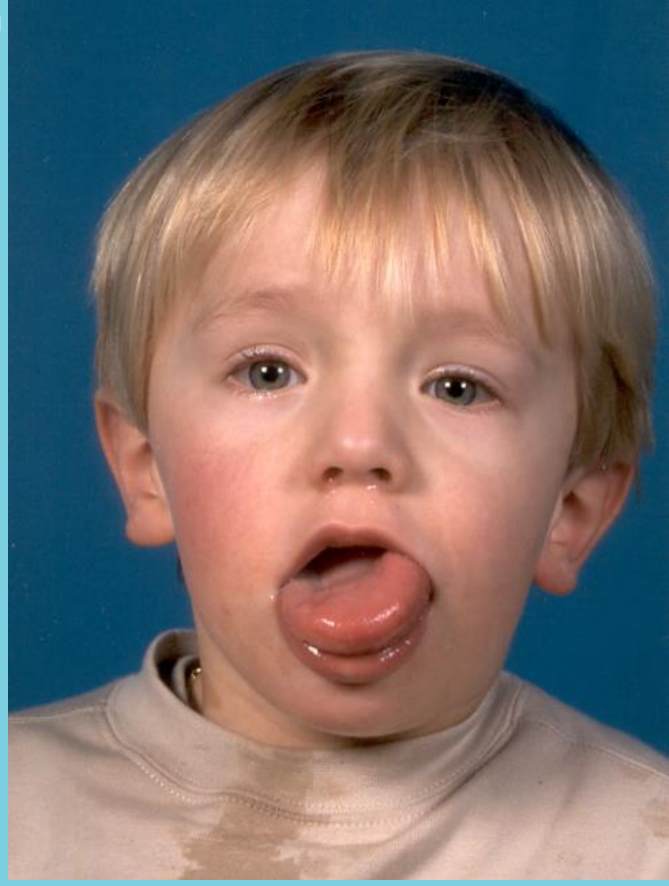
- - 0,5 cm diameter before puberty
- - 1,5 cm diameter after puberty

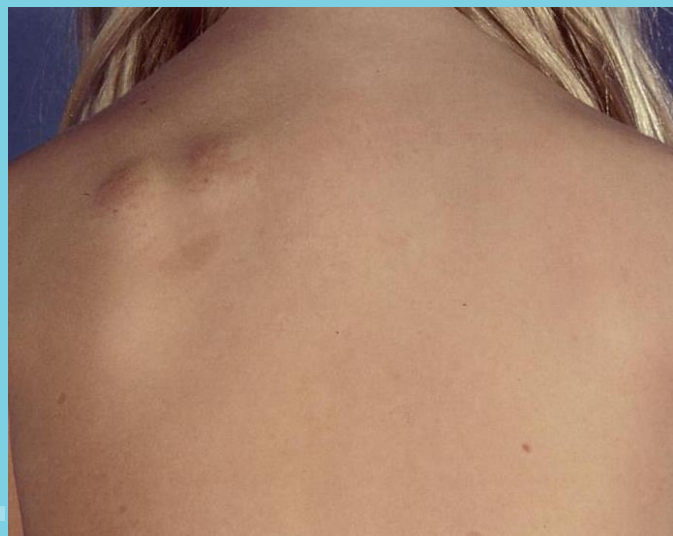
(often appear after 6 months of age)



Clinical diagnostic criteria NF1

2. Two or more cutaneous neurofibroma or one or more plexiform neurofibroma





Clinical diagnostic criteria NF1

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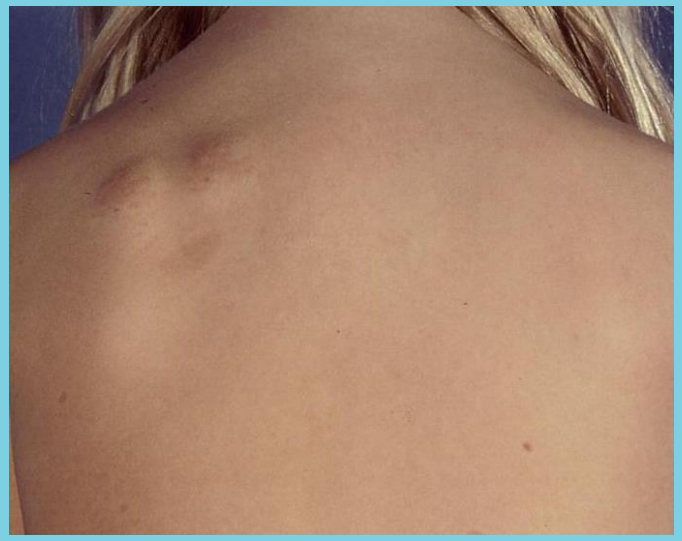

Appear after puberty, not of help for diagnosis at young age !

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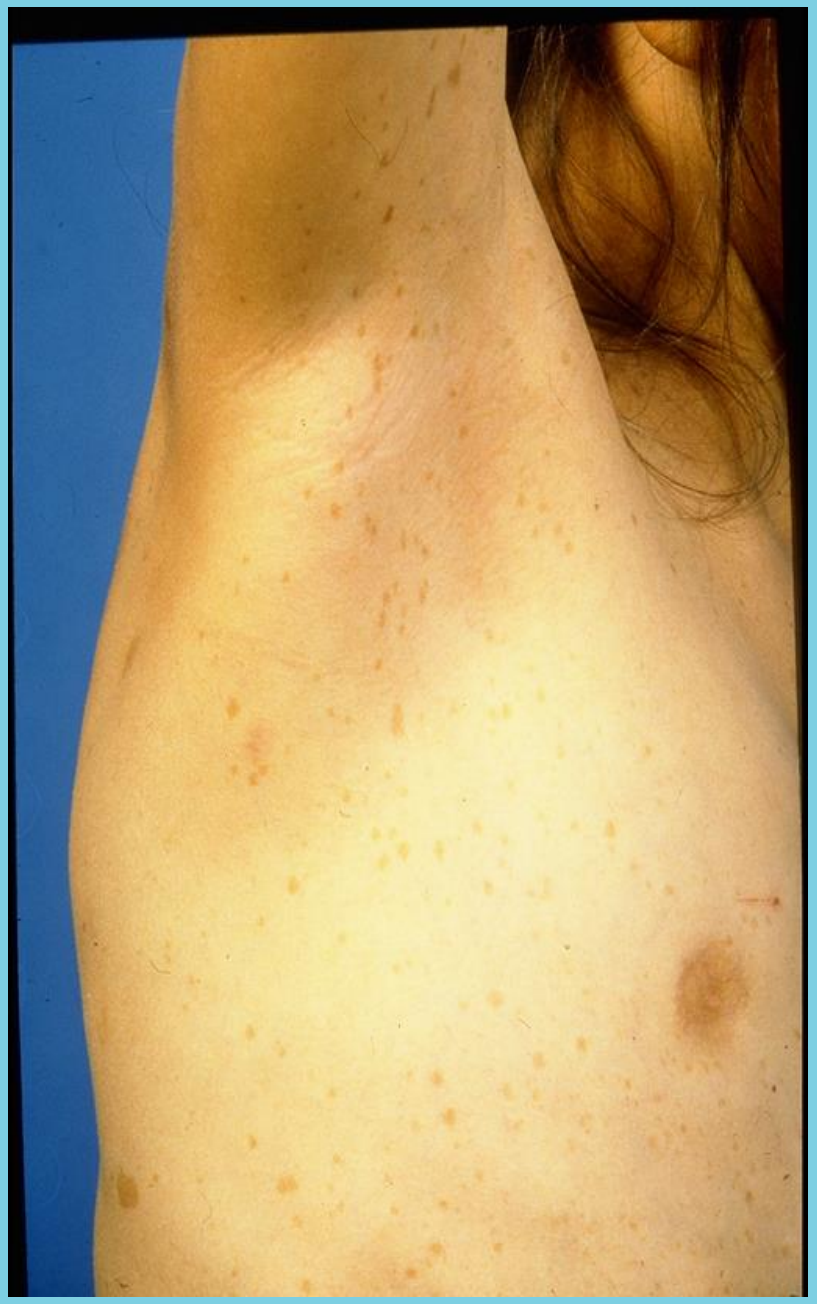
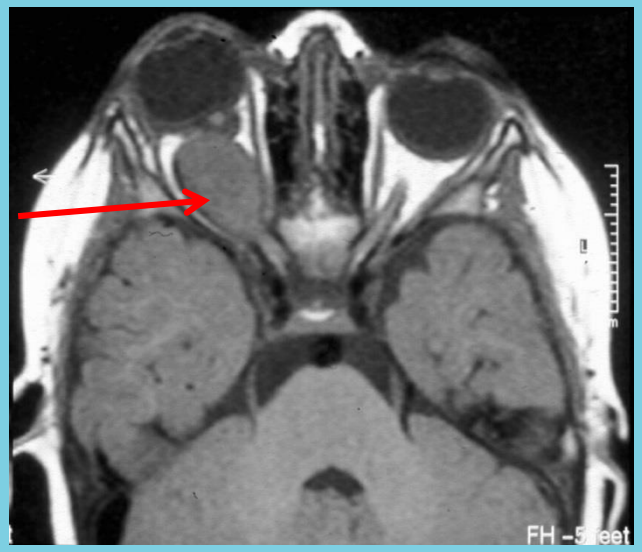
Clinical diagnostic Criteria NF1

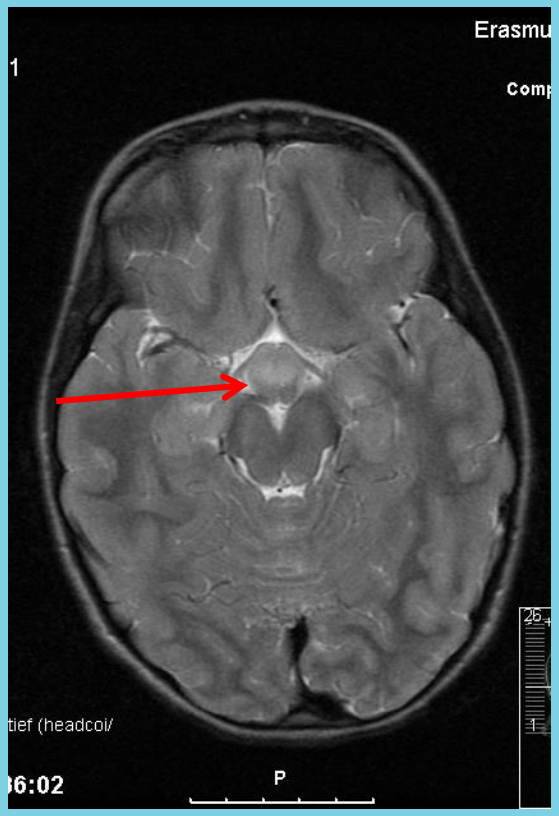
3. Freckling in the axillary or inguinal
   (children often > 6 years)

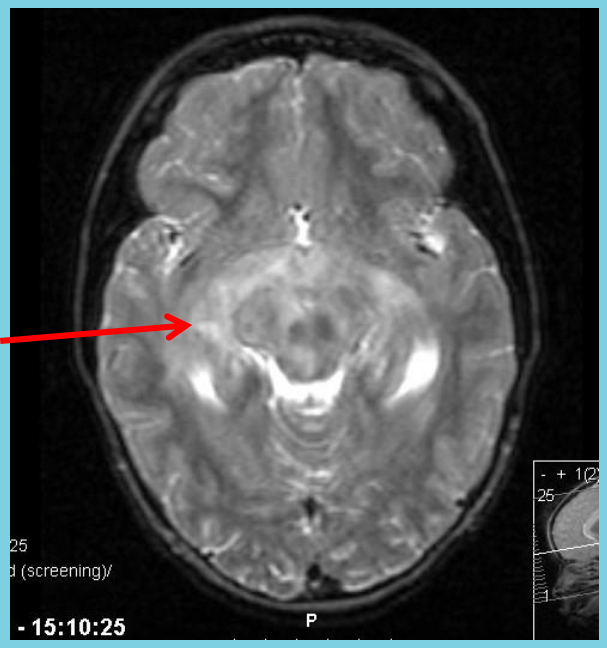


4. Optic pathway glioma (20% of chldren with NF1)

often asymptomatic







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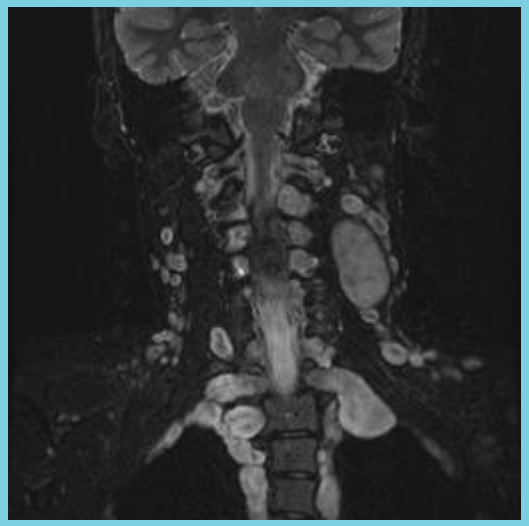
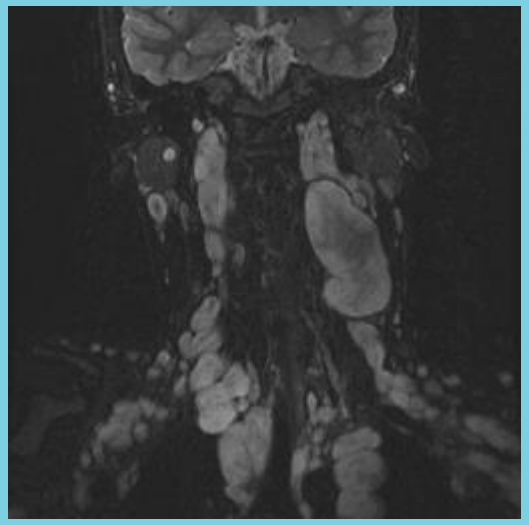
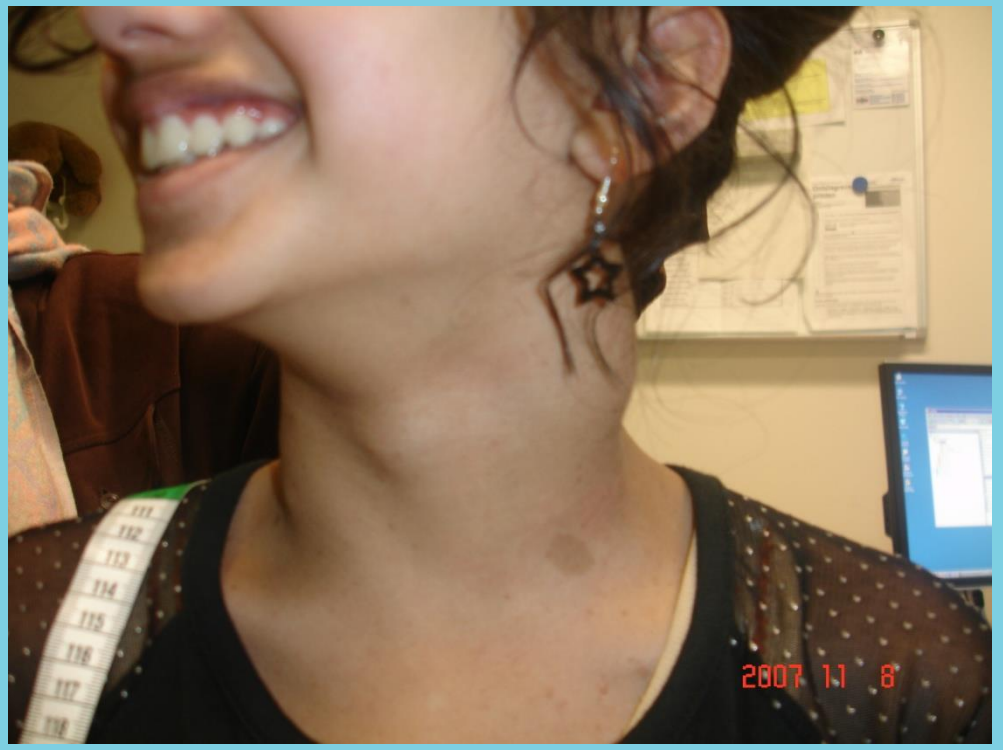
5. NF1: plexiform neurofibroma







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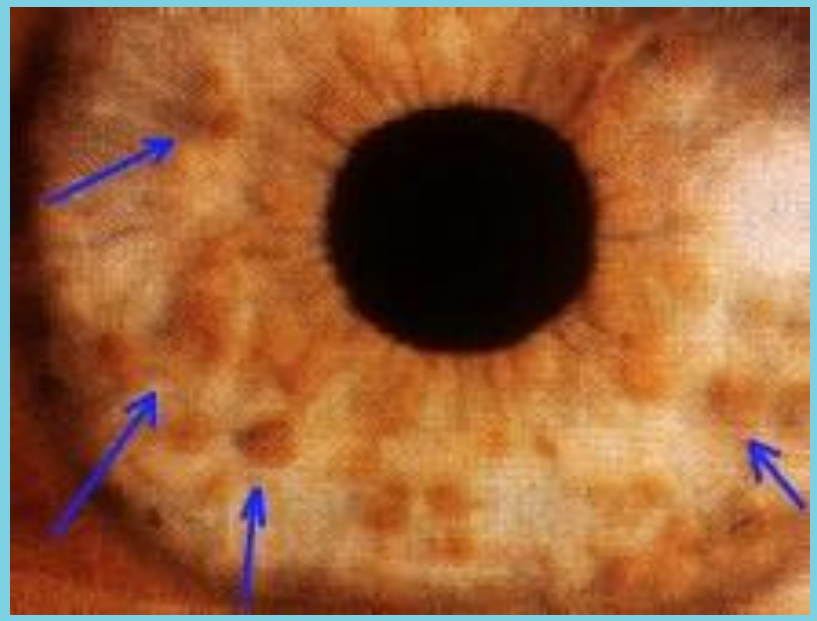
6. Two or more Lisch noduli

(iris hamartoma = mostly occur after age 10)



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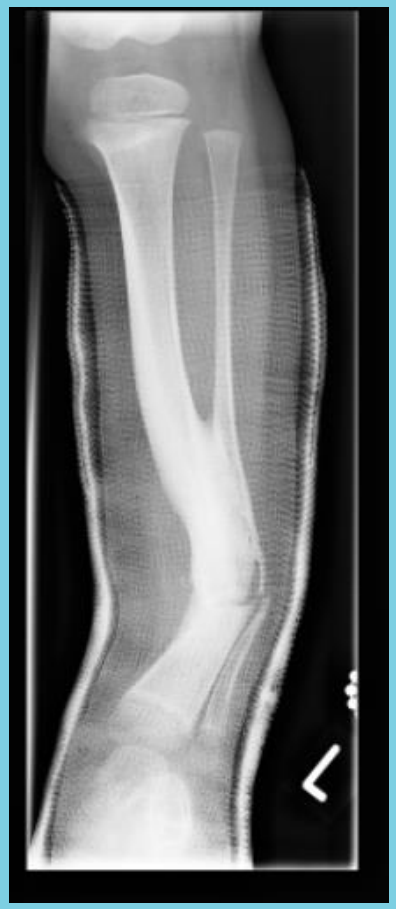
Clinical diagnostic criteria NF1

7. Skeleton dysplasia (dysplasia os sphenoidale or cortical thinning of long bones with or without pseudoarthrosis)



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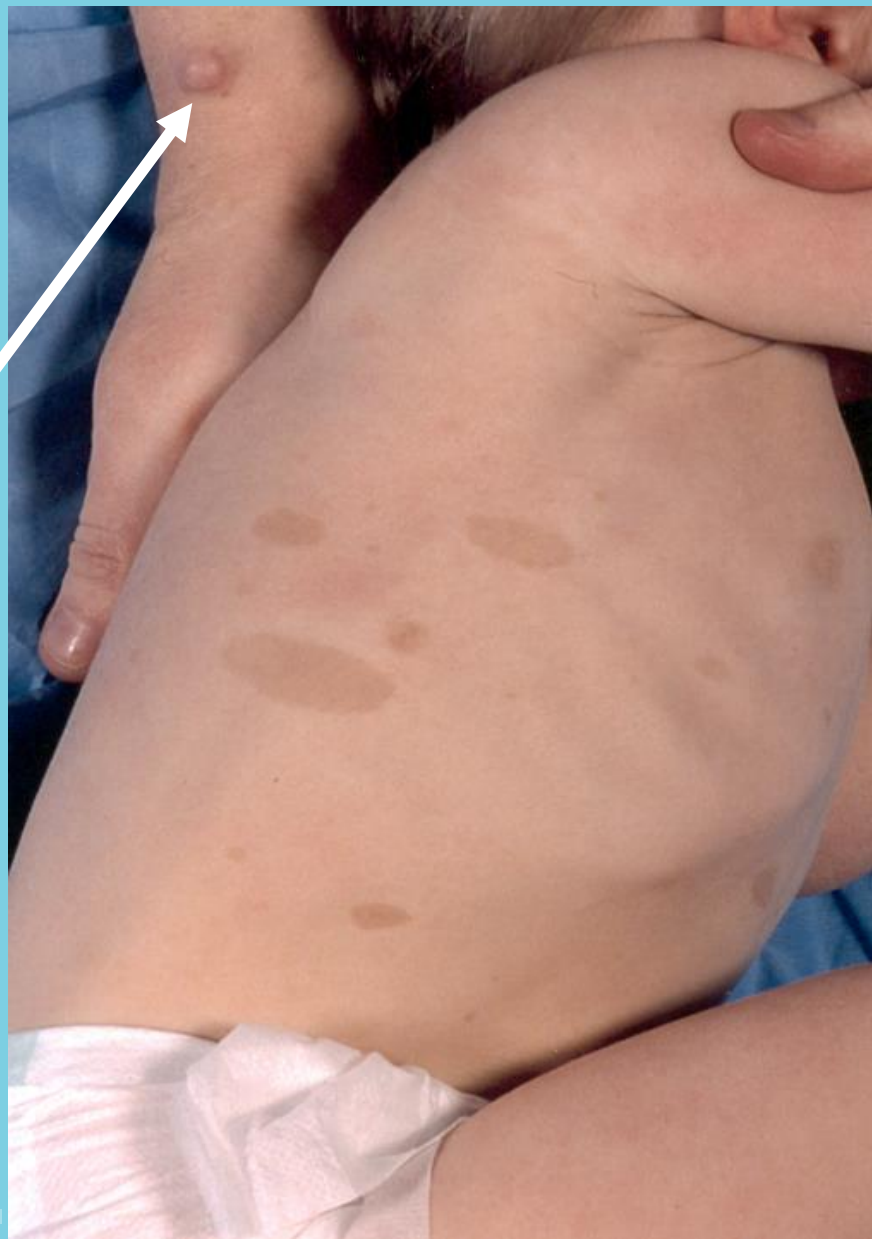
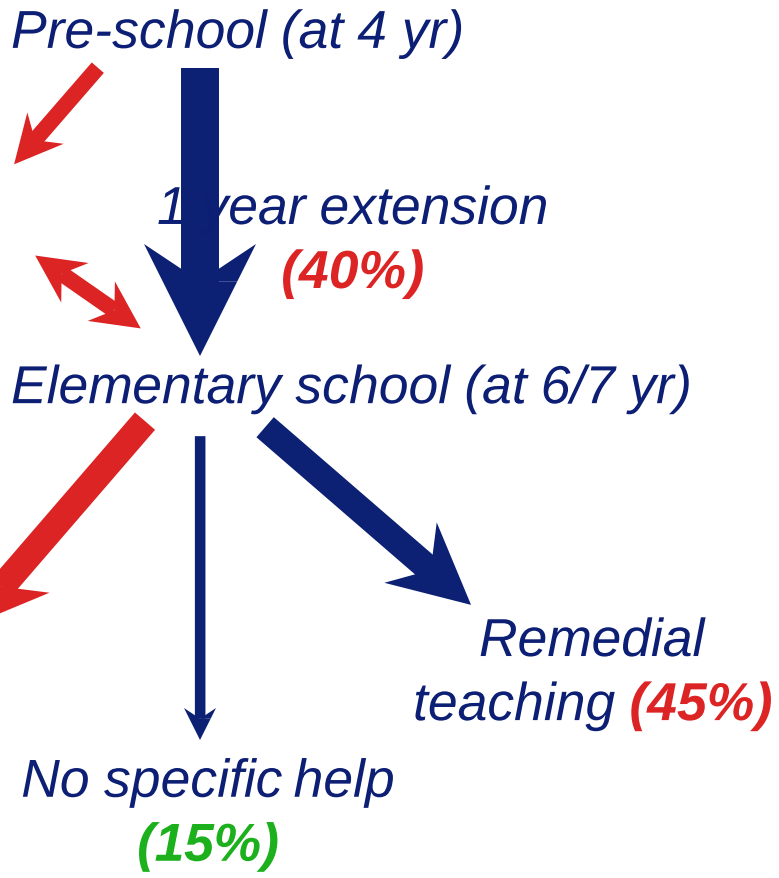
Clinical diagnostische criteria NF1

8. First grade family member with NF1



School performance of 86 Dutch NF1 children



Krab et al. J. Child Neurol. 2008; 23:1002-10

Most severe burden in children with NF1

- *Average 10-15 points lower IQ*
- *Visuospatial impairment*
- *Attention-deficit-hyper-activity disorder (up to 40%)*
- *Problems in executive functioning*
- *Fine and gross motor coordination deficits*

(Systematic review: Lehtonen et al., 2013)

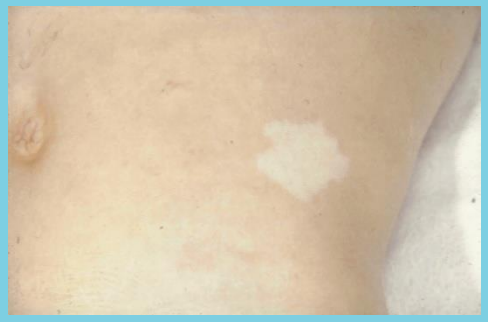
- ***21-25% autism spectrum disorder***

(Garg et al., Pediatrics; Plasschaert et al., J Autism Dev Disord.)

Tuberous Sclerosis Complex

- Autosomal dominant, 67% new mutations (incidence 1:10.000)
- 100% penetrance, variable expression
- TSC1 gene: chromosome 9q34
    - Hamartine
- TSC2 gene: chromosome 16p13.3
    - Tuberine
- Hamartine-tuberine complex/ negative regulator of cel cycle

Adenoma sebaceum



Hypomelanotic maculae

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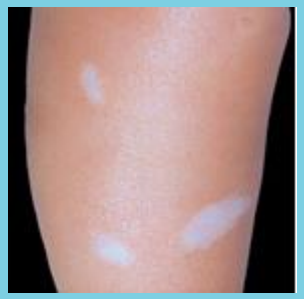
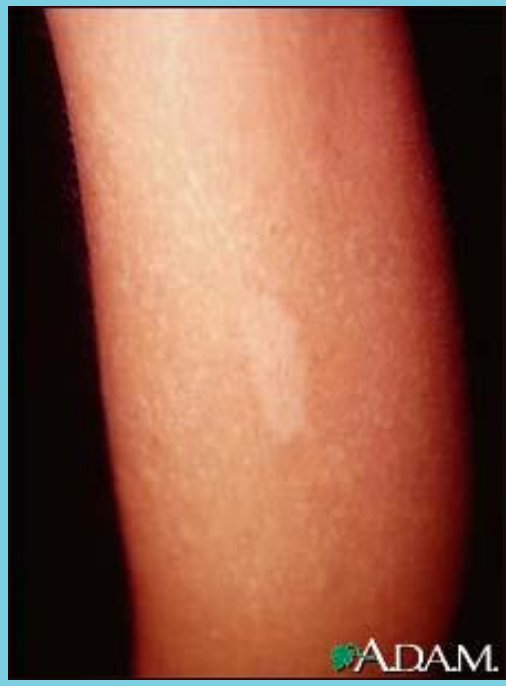
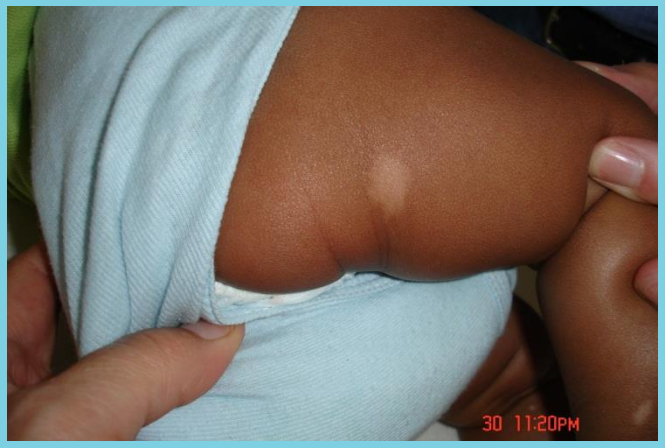
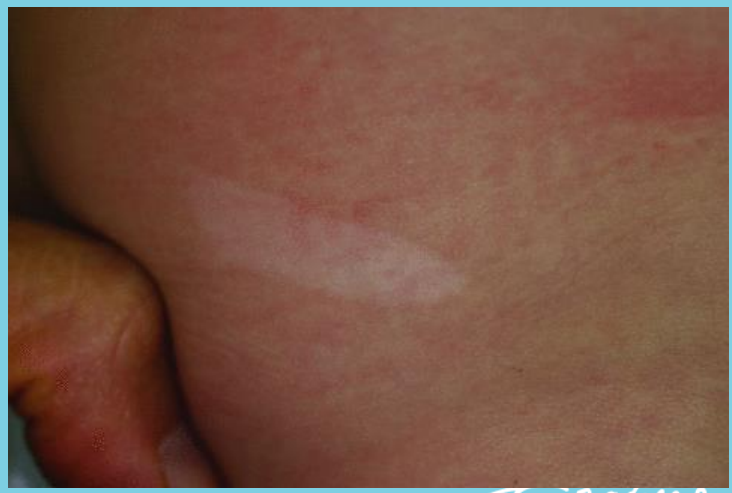
TSC: hypomelanotic maculae

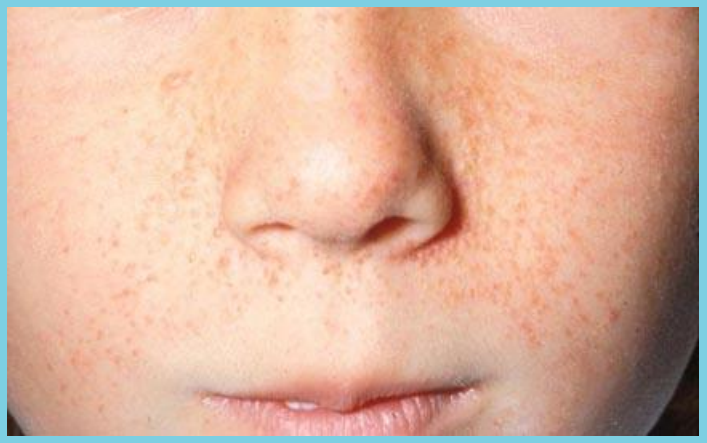








Angiofibromata in TSC patients



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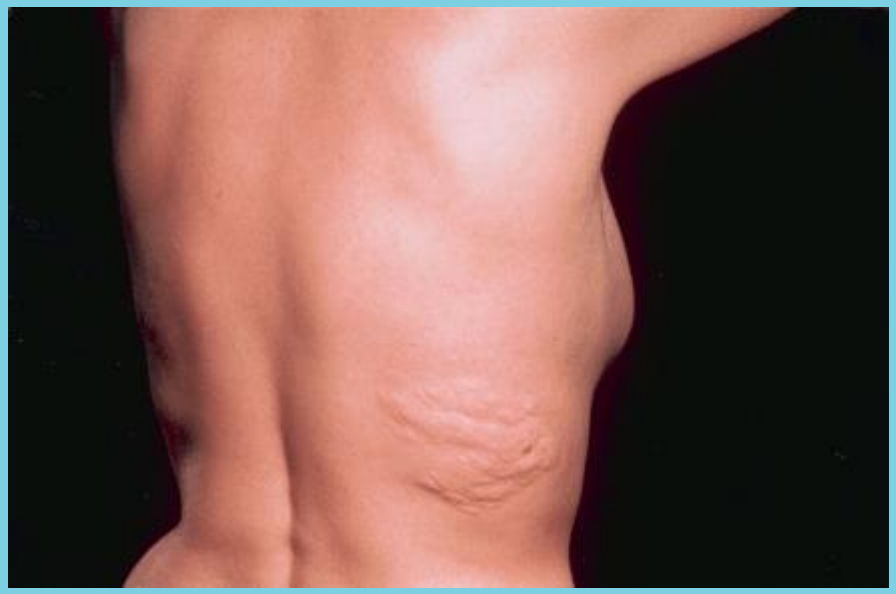
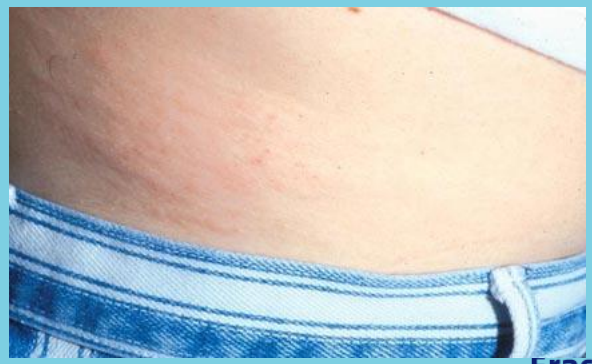
Othe cutaneous spotd in TSC

- Plaques
- Shagreen patch/ Peau de chagrin





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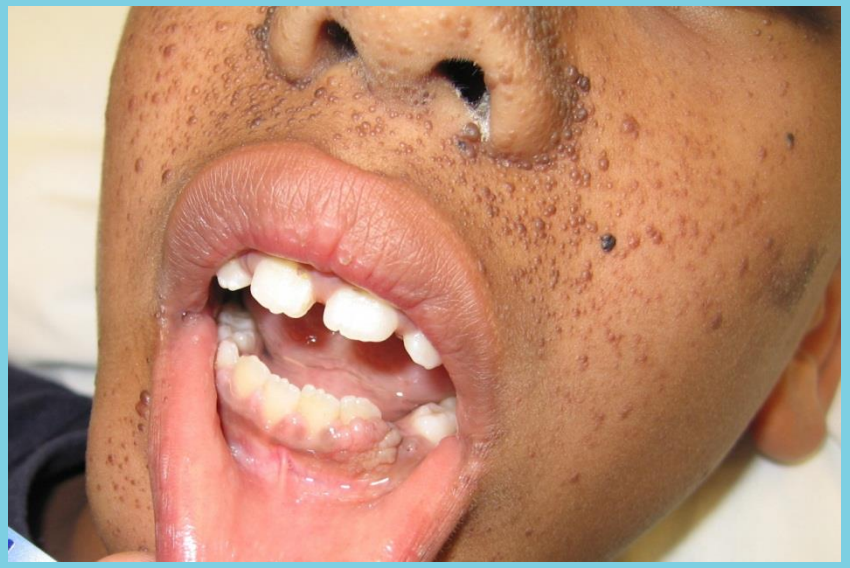
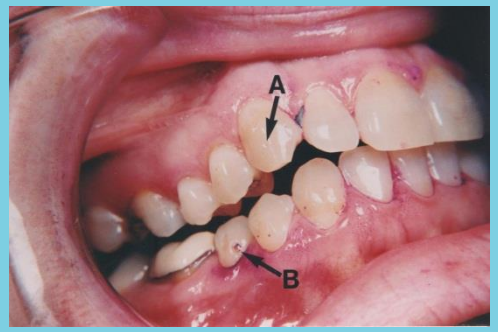
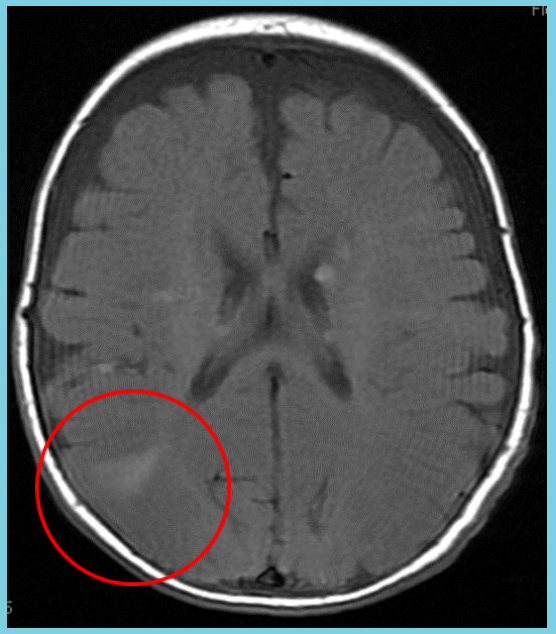
Abnormalities mouth and nails in TSC

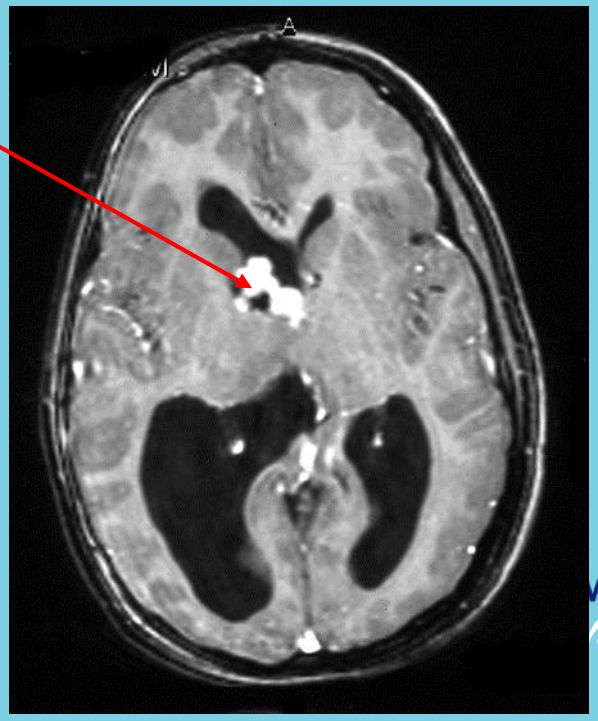




CZS pathology in TSC

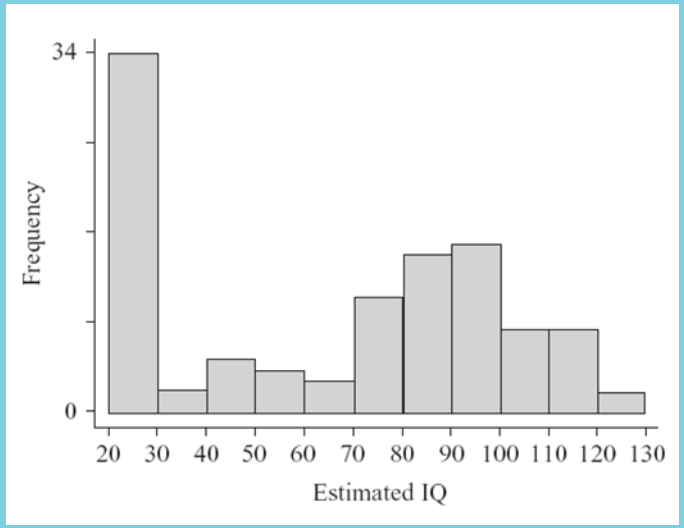
- Cortical tubers (>80 %)
- Subependymal noduli (80%)
- Subependymal giant cell tumor (6-14%)
  - Benign/ 10-30 jaar





60% of TSC patienst have a cognitive impairment

- learning deficits
- ADHD
- autism



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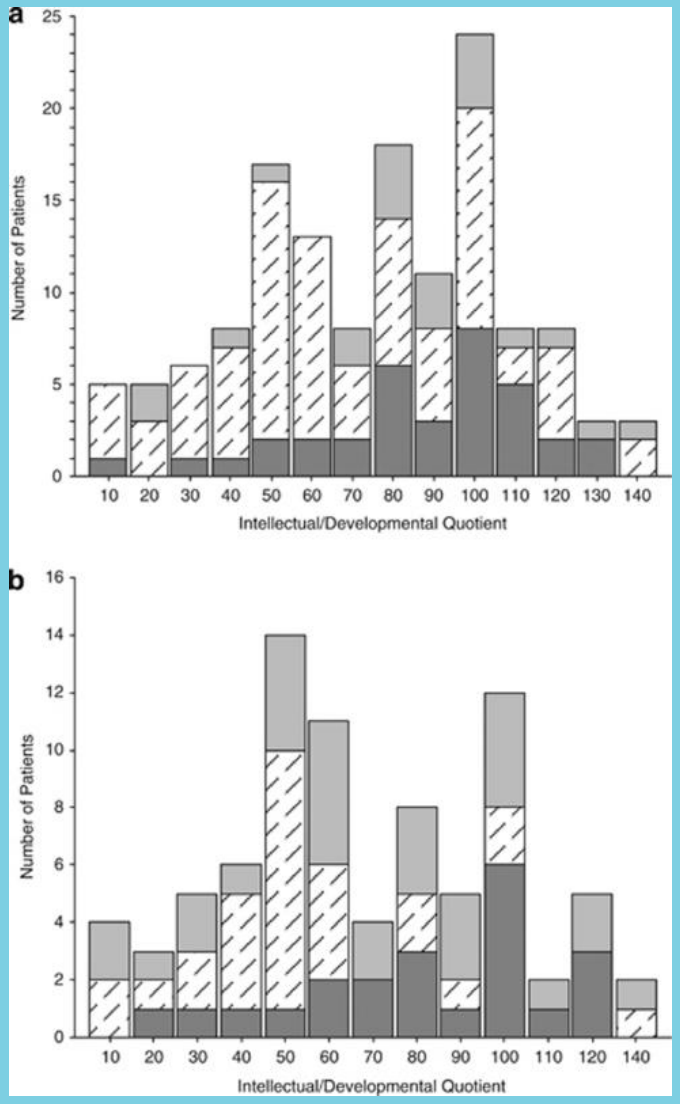
Cognitive restricitionion TSC1 and TSC 2



TSC1

TSC2

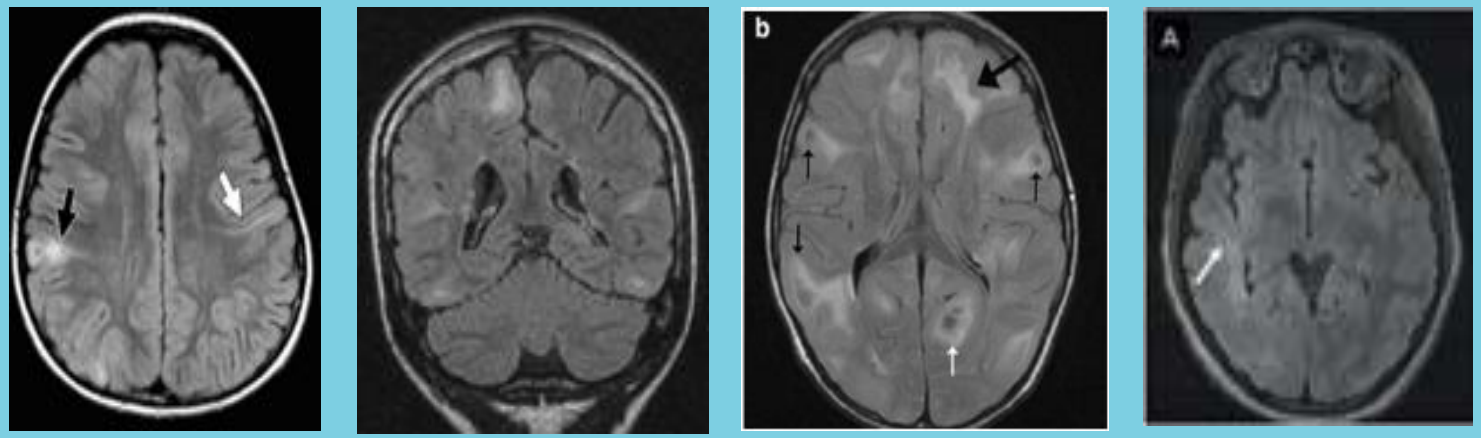
Van Eeghen et al. Eur J Hum Genetics

Erasmus MC

Severity of mental retardation in TSC dependent of

- Cerebral abnormalities
  - Number of tubers,
  - migration lines

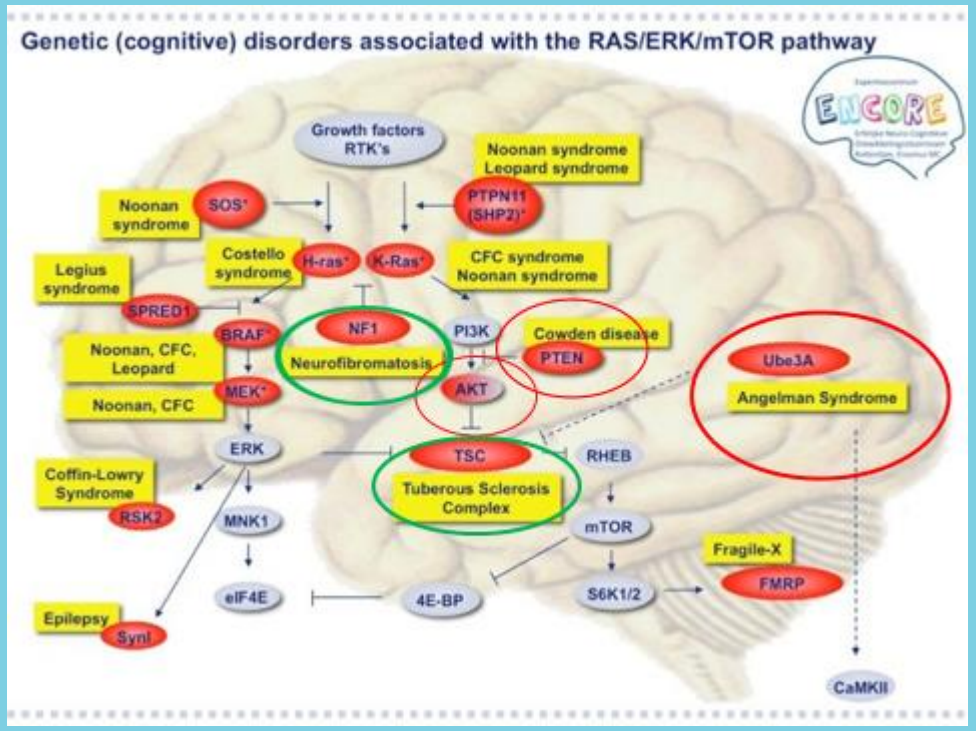
- Epilepsy (age at onset, seizure typem response to treatment)
-



Jansen Neurology 2008, van Eeghen J Ped Neurradiology 2013

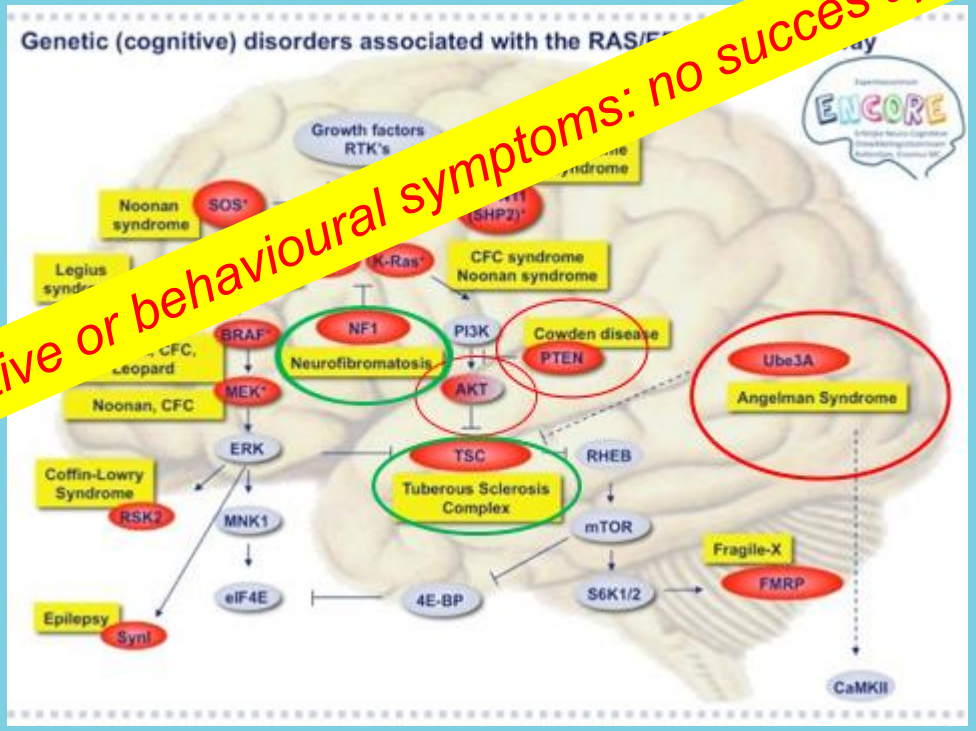
Erasmus MC

Knowledge of molecular pathways involved in genetic cognitive disorders leads to new treaments of the symptoms of these syndromes



Erasmus MC

Knowledge of molecular pathways involved in genetic cognitive disorders leads to new treatments of the symptoms of these syndromes



In respect to reversal of cognitive or behavioural symptoms: no succes up to now

Erasmus MC

Conclusion: clinical observation gives the most important clues to the cause of mental retardation

- Skull circumference and shape
- Skin abnormalities
- locomotion
- Behaviour
- Dysmorfic features

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Amsterdam 2016

1-5 May - ICNC2016.org

Bridging Worlds – Child Neurology from a Global Perspective