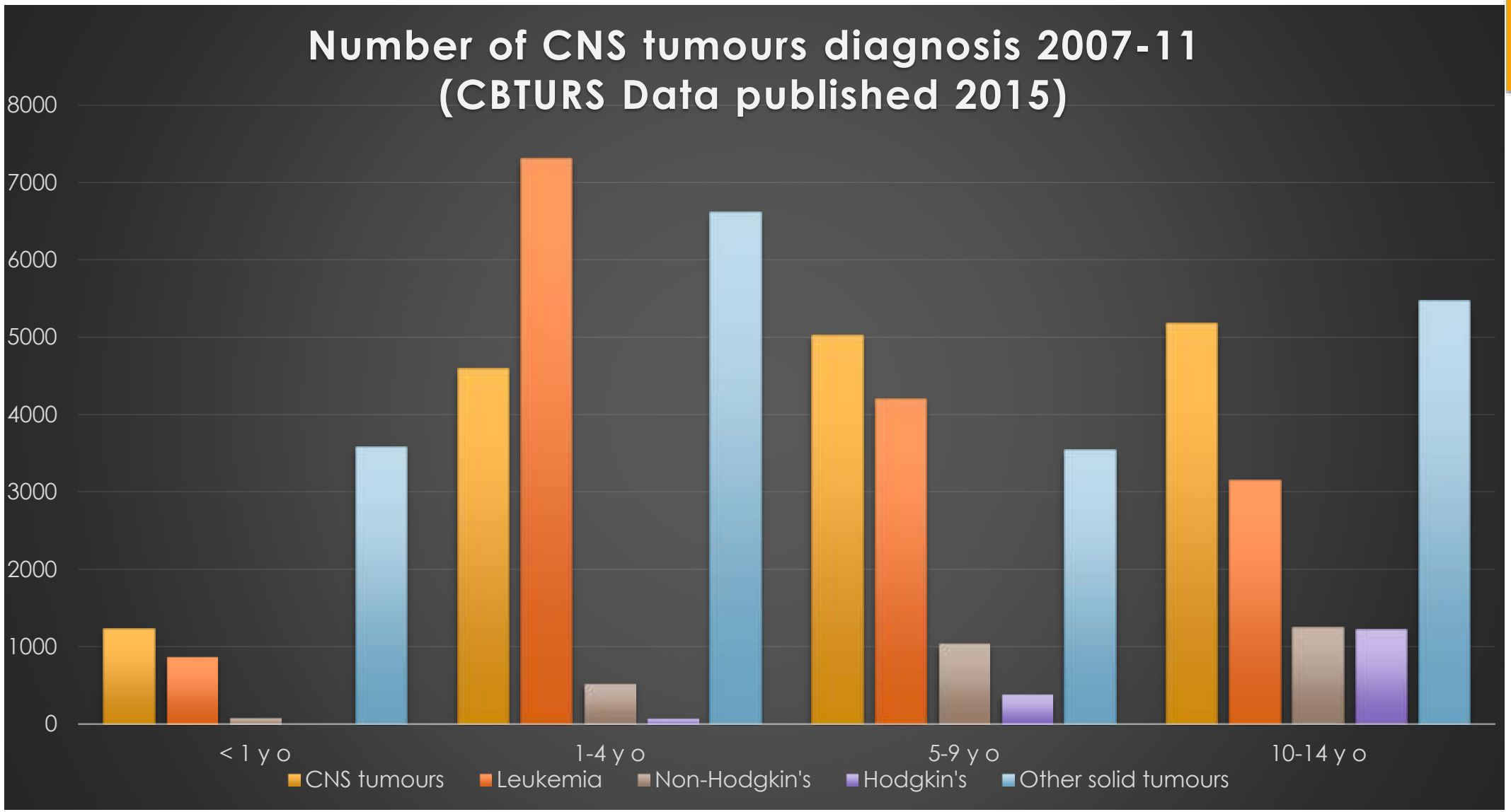
Pediatric brain tumours

DIAGNOSIS IN PRIMARY CARE

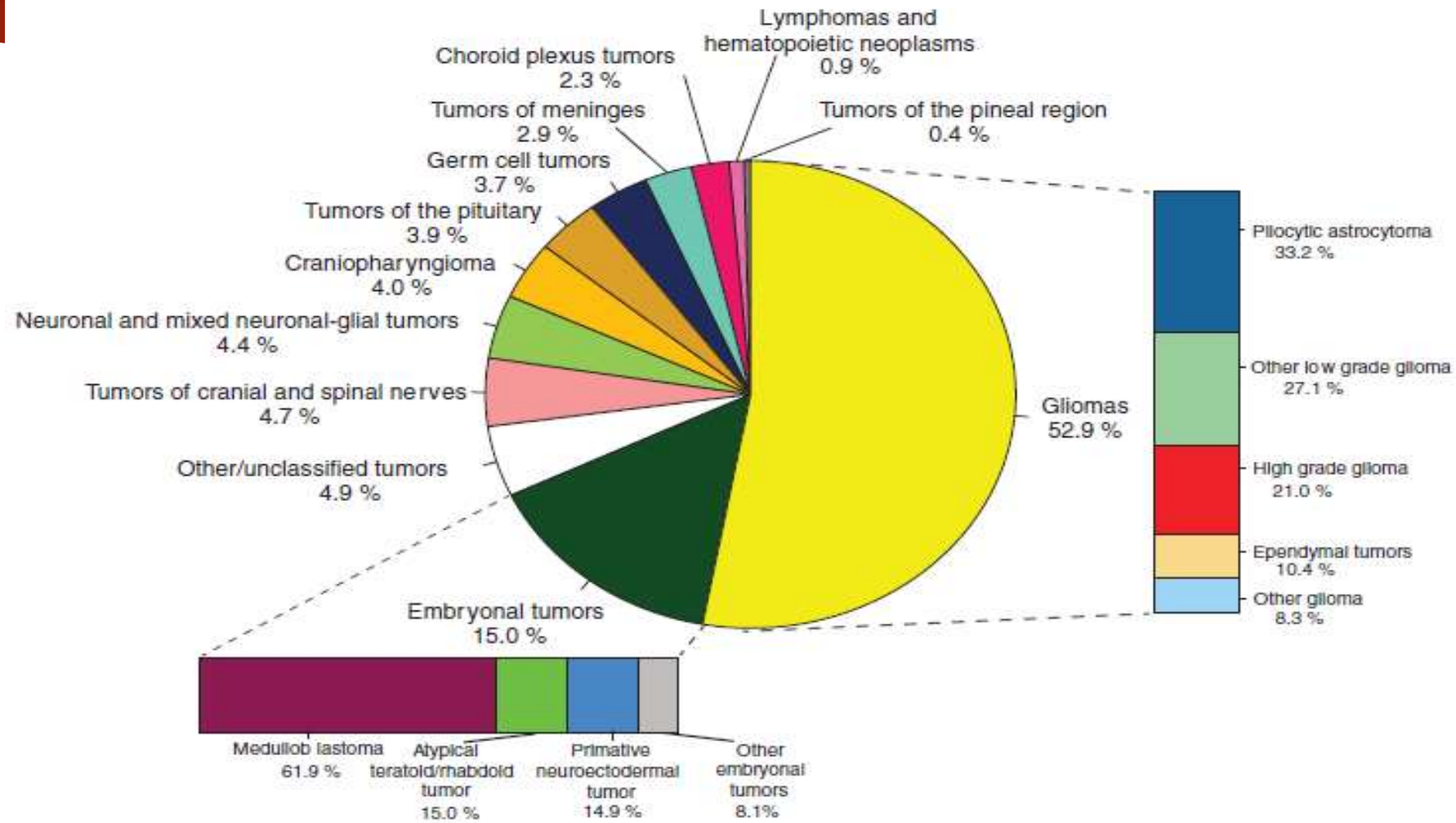
Overview:

- Most common solid tumour in children and most common cancer in < 1 yr olds, and 5-14 yr olds. (CBTRUS 2015)
- Challenging pathology:
  - **Early diagnosis**
  - Management:
  - Patient related factors : young age, developing brain, different biology than in adult
    - Treatment challenges:
      - **Surgical:**
      - location and accessibility, risk of collateral injury
      - complex and prolonged procedure often in very small children, sometimes requiring second look surgery
      - **Chemo-radiation treatment**:
      - Significant side effects with radiation in young children especially <5 yr olds, risk of developmental delay, long term cognition, development of other tumours
      - Limited availably of chemotherapy and "collateral damage"


Number of CNS tumours diagnosis 2007-11
(CBTURS Data published 2015)
8000
7000
6000
5000
4000
3000
2000
1000
0
< 1 y o
1-4 y o
5-9 y o
10-14 y o
CNS tumours
Leukemia
Non-Hodgkin's
Hodgkin's
Other solid tumours

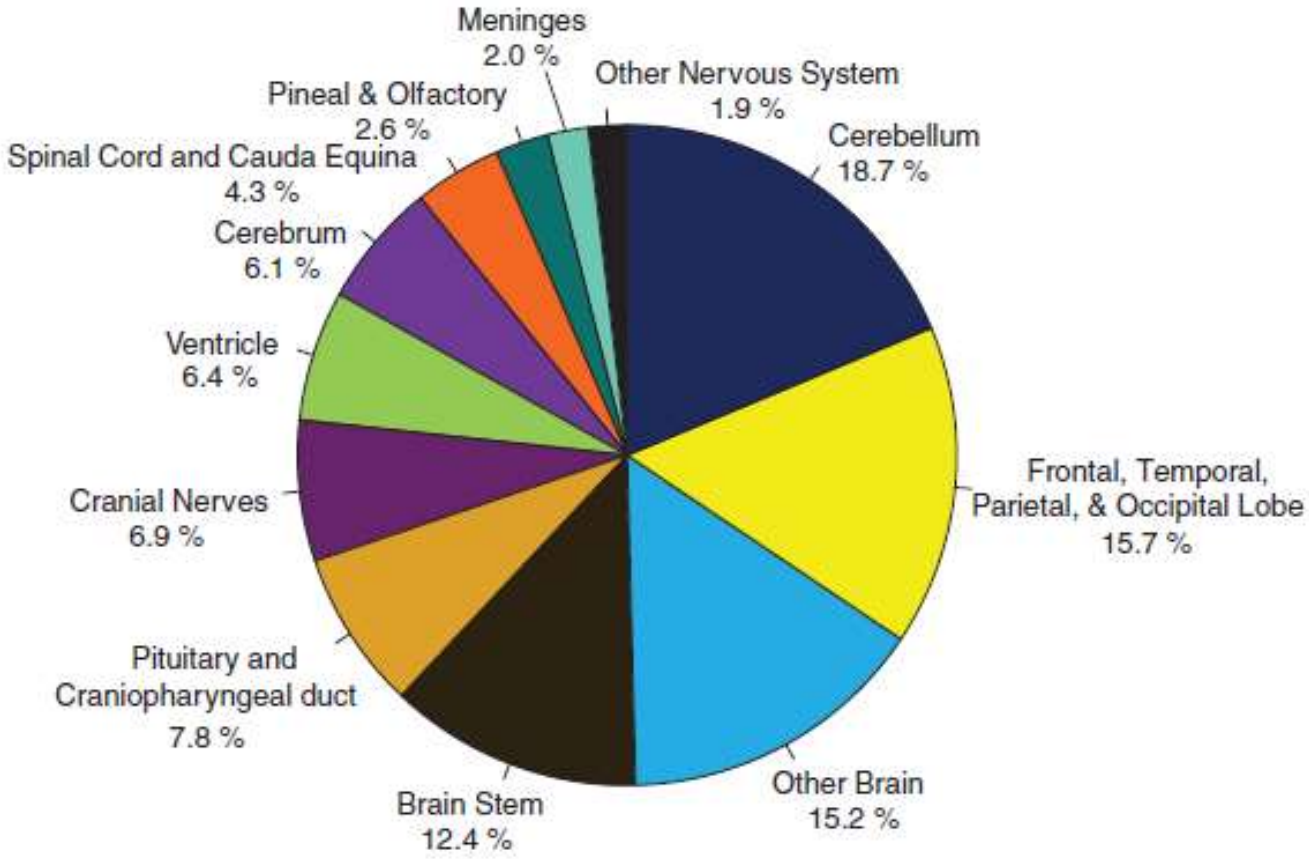
- SCH annual stats:
  - 40-45 new brain tumour cases
- In NSW :
  - 85-95 new tumours annually

Quinn T. Ostrom: Alex's Lemonade Stand Foundation Infant and Childhood Primary Brain



Distribution of All Primary Brain and CNS Tumors by Histology Groupings (0–14 Years) (N = 16,044) (CBTRUS 2007–2011)

Location of brain tumour seen in children:

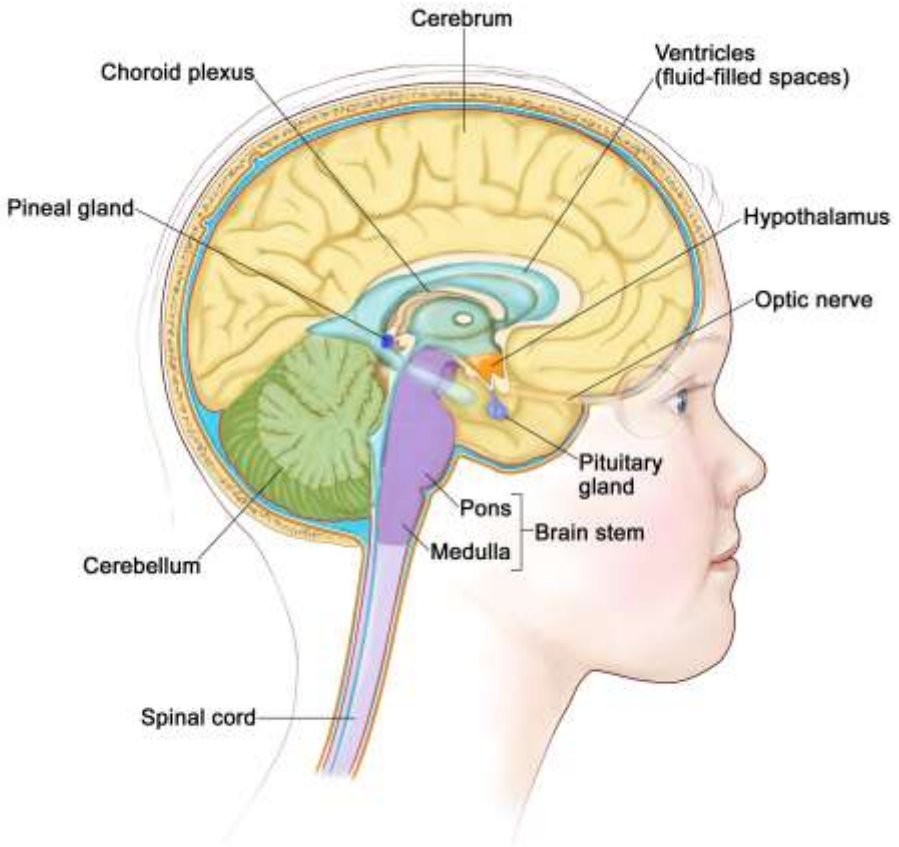


Distribution of All Primary Brain and CNS Tumors by Site (0–14 Years) (N = 16,044) (CBTRUS 2007–2011)

Posterior fossa:

- Pilocytic astrocytoma
- Medulloblastoma
- Brain stem gliomas
- Ependymoma

- **Cerebral gliomas (low and high grade)**
- mixed neuronal tumour
- Hypothalamic/optic glioma
- Sellar region tumours:
  - Craniopharyngioma
  - Pituitary tumours
- Ventricular tumours:
  - Choroid plexus tumours
- Pineal region tumours
  - Germ cell tumours
  - Pineal tumours



Challenges in pediatric brain tumours:

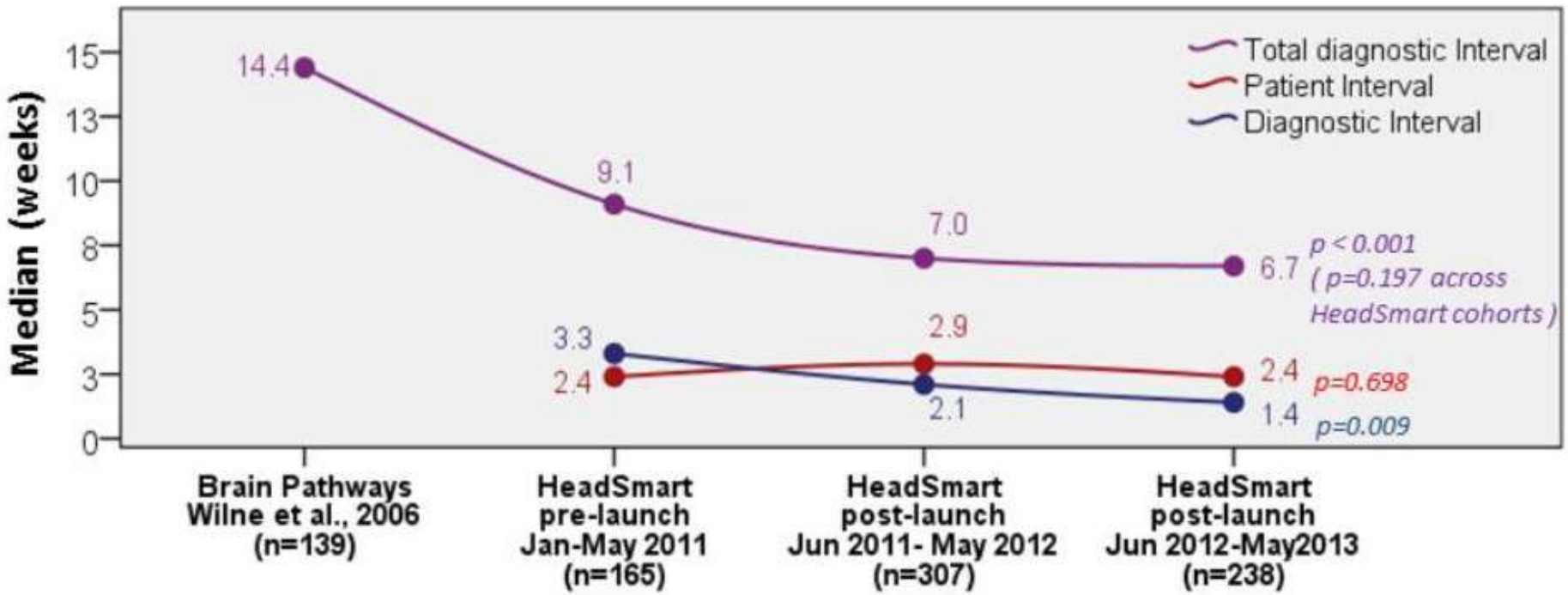
- Early diagnosis
- Surgical management
- Adjuvant treatment for long term cure/ remission

Importance of early diagnosis:

- Questions about early diagnosis:
  - The first concern and long term guilt for most parents
- HeadSmart campaign in UK:
  - Shown reduction of "time to diagnosis" from 9.1 weeks to 6.7 weeks
  - ?Possible reduction in the impact of neurological function impairment, eg. visual impairment
  - ?reduction of side effects of treatment
  - ?Reduce dissemination, e.g. Medulloblastoma

THE BRAIN PATHWAYS GUIDELINE:
A GUIDELINE TO ASSIST HEALTHCARE PROFESSIONALS IN THE ASSESSMENT OF CHILDREN WHO MAY HAVE A BRAIN TUMOUR

Version 2 February 2017
(revision of version 1 Published 2008)



Development of brain tumours:

- Predisposing factors:
  - NF 1/2
  - Tuberous sclerosis
  - Previous cancers
  - Previous radiation
  - Family hx of cancers

Signs and symptoms:
presentation depends on age

AGE GROUPS:

- UNDER 2'S
- UNDER 5'S
- 5-11 YR OLDS
- TEENAGERS

Nausea and vomiting:

Reassure but monitor:

- Duration <2 weeks
- Other concurrent signs of infection
- HC is tracking normally
- No other associated symptoms or signs
- Responsive to Gastro-esophageal reflux treatment

- ***Review weekly! Symptoms, HC***
- ***Always do basic neuroexam: alertness and tracking, H/C, gait and balance, limb movement, eye movements***

Scan or refer:

- Persistent >2 weeks
- Concerning features:
  - In the mornings, or wakes child up
  - Associated with: headaches, dehydration
- No other signs of infection
- Not responding to treatment
- Other neurological symptoms or signs
- ***HC deviation from normal growth***

Headaches:

Monitor:

- <2 weeks
- Other infection associated symptoms

Scan or refer

- >2 weeks
- Occurring most days
- Associated with vomiting, confusion, lethargy, less alert, disorientation
- Morning H/A
- Waking from sleep
- Other symptoms that could be associated with intracranial pathology: eye signs, change of behavior, gait snd motor dysfunction

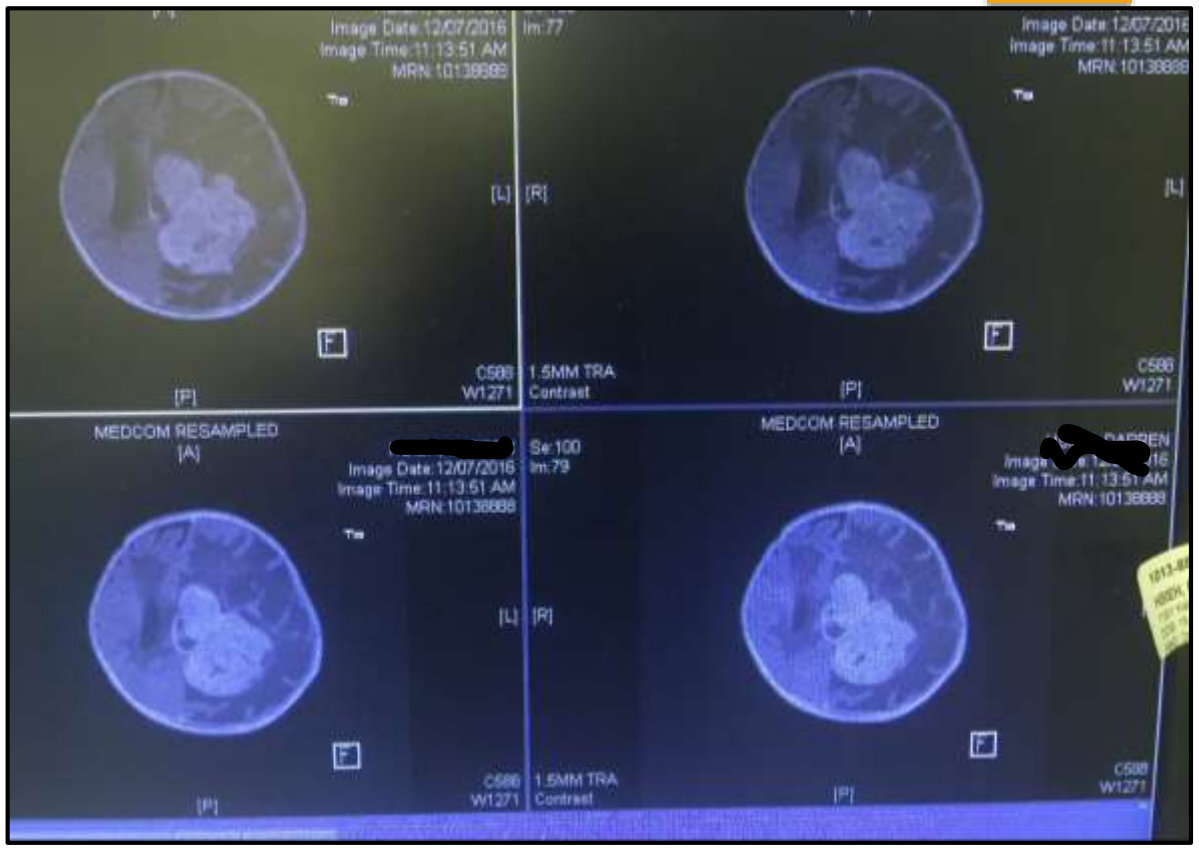
Signs and symptoms:

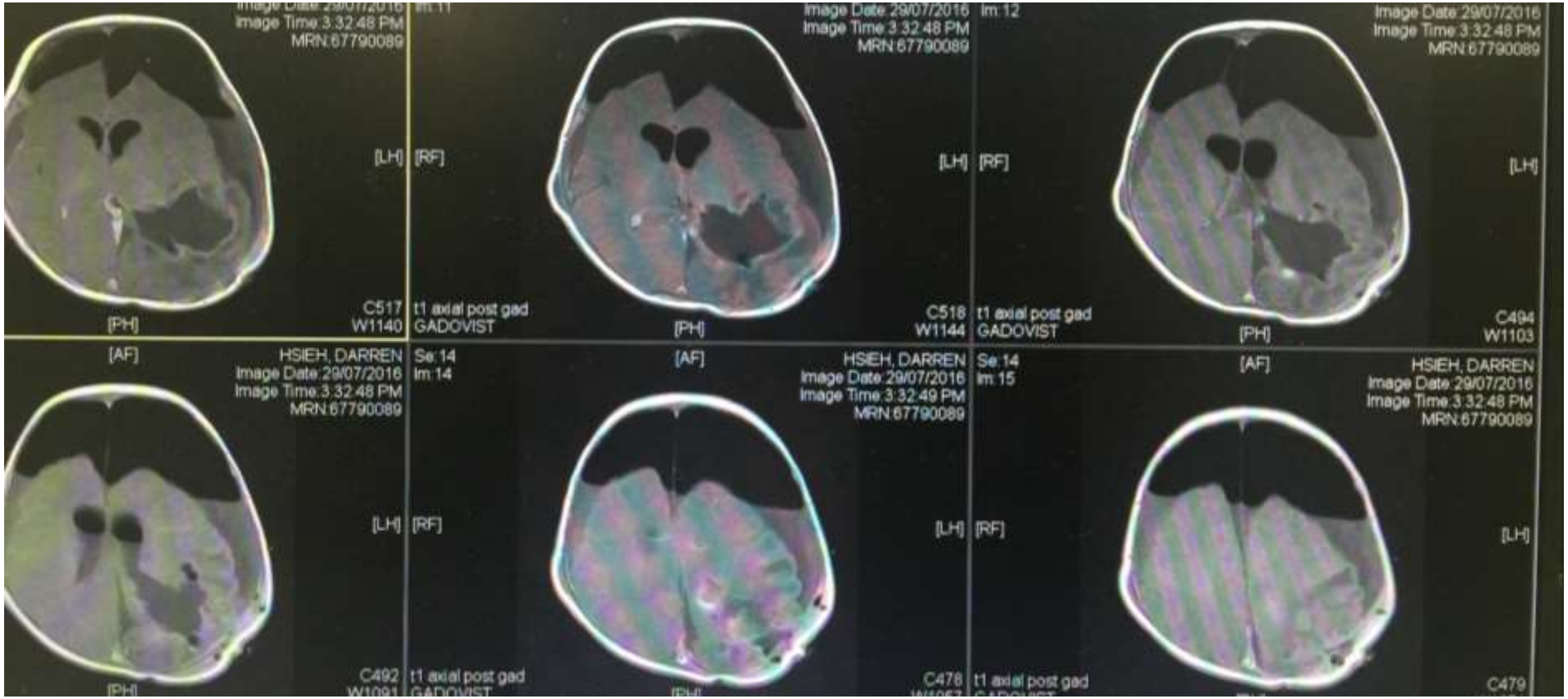
- Under 2's:
  - **Persistent Nausea and vomiting**
  - **Increased head circumference**
  - **Irritability**
  - **Failure of thrive**
  - Asymmetrical limb movements
  - Abnormal eye movements
    - (inability to follow objects)
    - Squints are common, assessment by specialist is indicated on initial dx
  - Seizure (partial seizures)

3 months old boy

Well

Noted rapid increase in HC

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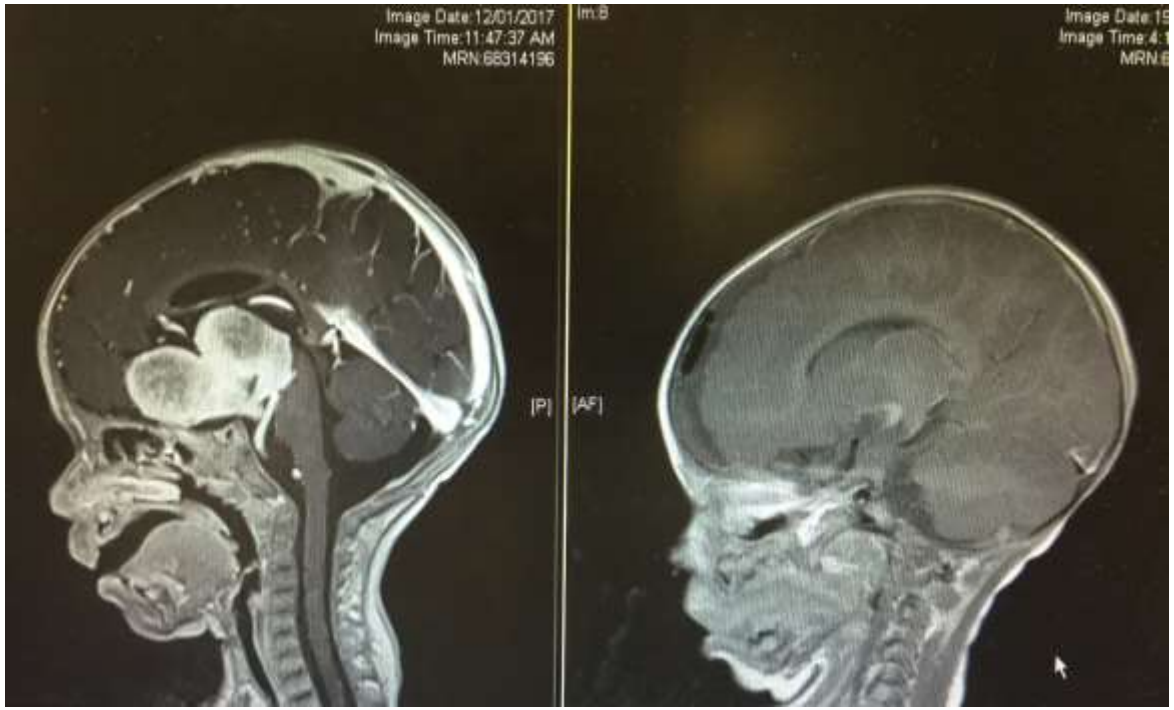
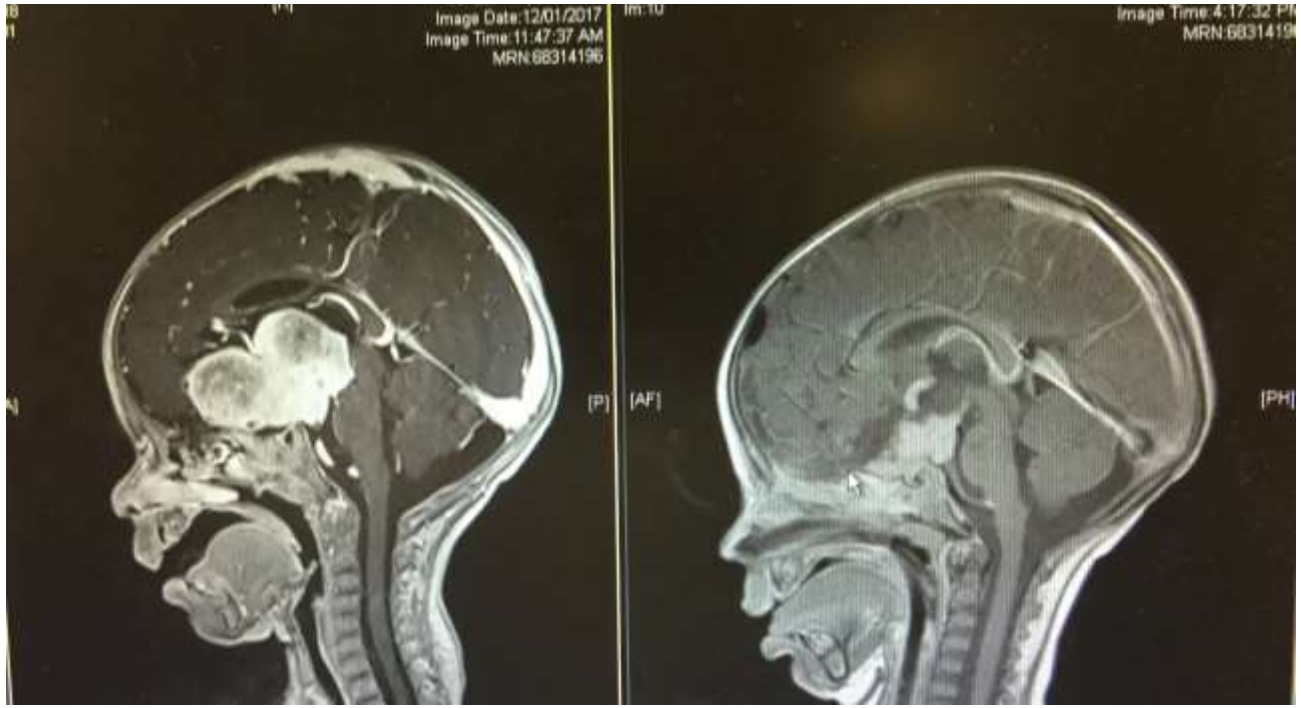


4 months old noted to have:

- Increased in HC
- Irritable
- On more detailed examination noted to have poor vision, dehydrated
- No signs or hx of NF

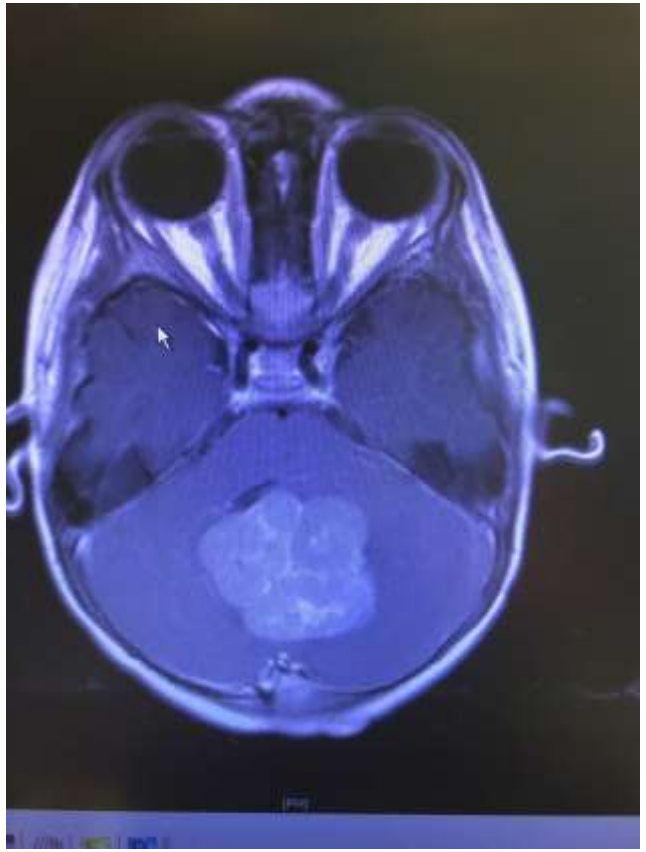


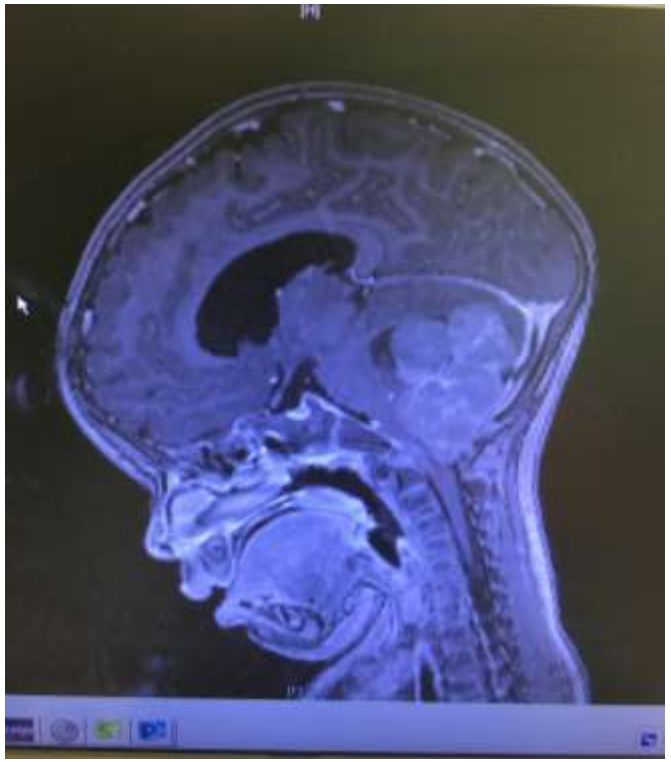
Presentation:

- Under 5's:
  - Persistent nausea and vomiting
  - Change of behavior: irritability, withdrawal, lethargy
  - Regression of motor function
  - Gait abnormality
  - Motor abnormality: Asymmetrical limb movements, facial asymmetry
  - Abnormal eye movement
  - Abnormal head position
  - seizure
  - ?headaches: can not report it, ? Holding head, withdrawal, nocturnal headaches

2.5 yr old girl

- 4 weeks of loss of balance
- Falling over easily
- Not playing and decreased interaction with peers
- Becoming more irritable at presentation





Presentation:

- 5 to 11-year-olds:
  - Recurrent Headaches
    - Headaches are common in school age, and rarely due to brain tumour in isolation
    - Look for associated symptoms
  - Visual symptoms: blurred vision, double vision
  - Cognitive decline or confusion
  - Other symptoms as discussed above.

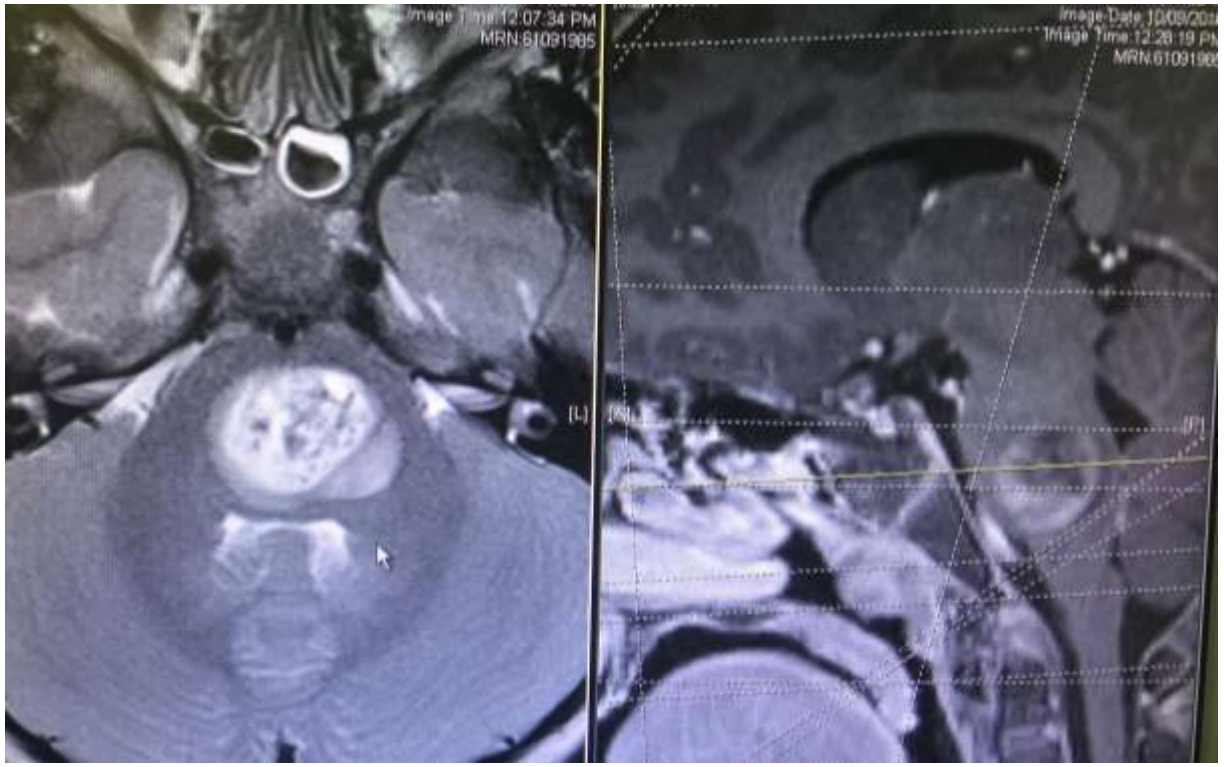
6 yr old boy

A week onset of slight limp

2 day hx of worsening of his gait

<24 of facial droop

In hospital rapid decline needing intubation

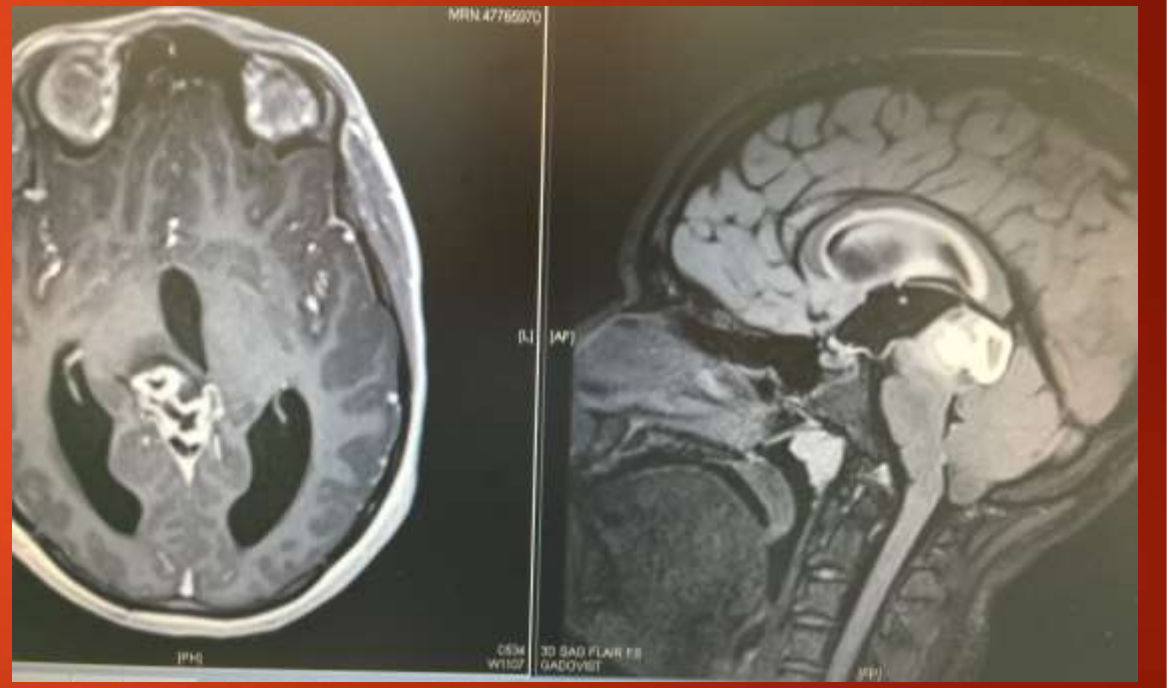


Presentation:

- Teenagers:
  - Delay or accelerated puberty
  - Endocrine dysfunction: Galactorrhoea, primary or secondary amenorrhroea
  - Abnormal growth
  - Confusion and cognitive decline
  - Headaches
  - Visual symptoms: blurred vision or double vision

14 yr old girl

- Soccer player
- At presentation had severe h/a and vomiting
- about 2 months hx of :
  - unable to run well
  - Also headaches on exertion which were progressively worsening
- <u>No visual signs or symptoms.</u>



- General concerning signs and symptoms:
  - Decrease level consciousness
  - Excessive thirst or urination
  - Normal neurological examination does not exclude presence of brain tumour!
    - If suspected
      - Detailed hx is crucial
      - plan a follow up!
      - Refer or discuss with specialists
  - ***Parental concern***!!!

Management:

Histopathological diagnosis:

- Multi-layered diagnosis with:
  - Morphological diagnosis
  - Molecular/genetic diagnosis
    - Has shown that pediatric gliomas are different to adult types
    - Leading to more accurate diagnostic
    - prognostic value
    - Improved treatment
    - Assessment of response to treatment

Treatment:

- Surgery, *when possible*, remains cornerstone of treatment for most brain tumours:
  - Diagnostic tissue, decrease ICP, decrease tumour bulk, may eliminate need for further treatment, improve prognosis
  - Complex
  - Complete excision may not be possible
  - Risk of neurological deficit, or life treathening
- Radiation therapy remains an important part of long term management but *has limitations:*
  - *Not usually given to under 5's*
  - *Long term risk of cognitive impairment*
  - *Endocrine disturbance*
  - *New tumours*
- Chemotherapy becoming more sophisticated and will become a major treatment modality:
  - Standard chemotherapy: Limitation due to side effects
  - ***Targeted therapy***

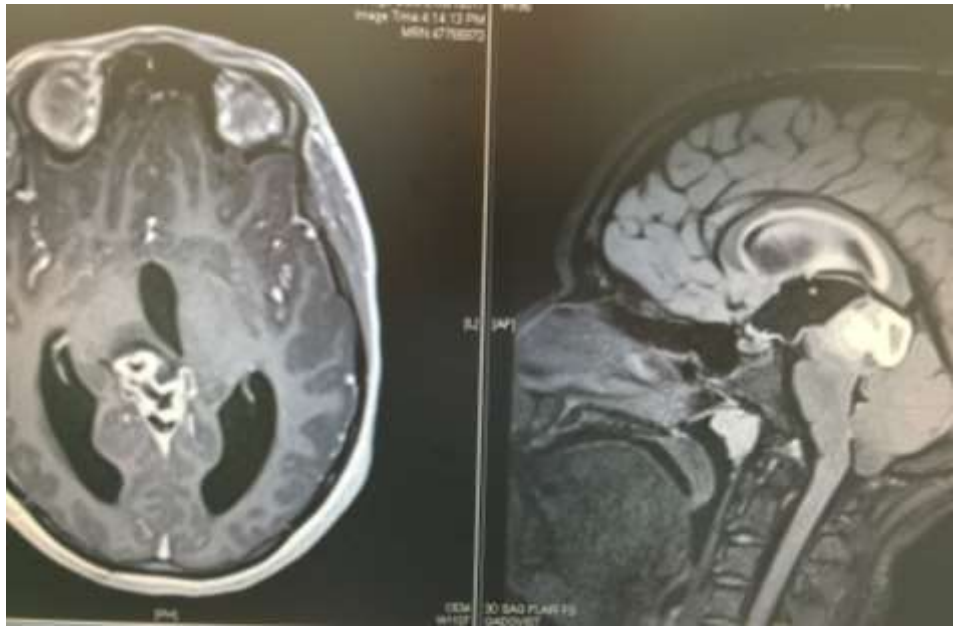
Targeted therapies:

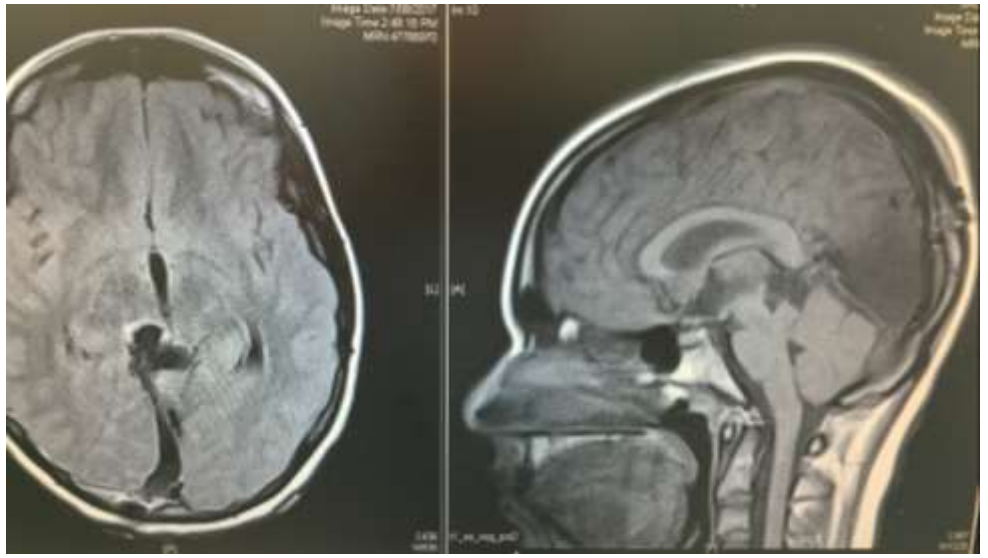
- Targeted drugs zero in on some of the changes that make cancer cells different. They target specific areas of the cancer cell that allow the cell to grow faster and abnormally. There are many different targets on cancer cells and many drugs that have been developed to attack them.
- Targeted drugs can work to:
- **Block or turn off chemical signals** that tell the cancer cell to grow and divide
- **Change proteins** within the cancer cells so the cells die
- **Stop making new blood vessels** to feed the cancer cells
- **Trigger immune system** to kill the cancer cells
- **Carry toxins to the cancer cells** to kill them, but not normal cells

Value of molecular diagnostics

Example:

- Radiologically concerning due to central necrosis
- Intra-operative thrombosed vessel and necrosis
- Histologically necrosis and few mitosis
- Chromosomal study showed "KIAA1559-BRAF fusion" associated with diagnosis of "**pilocytic astrocytoma"**





"Glioma cells are highly sophisticated"

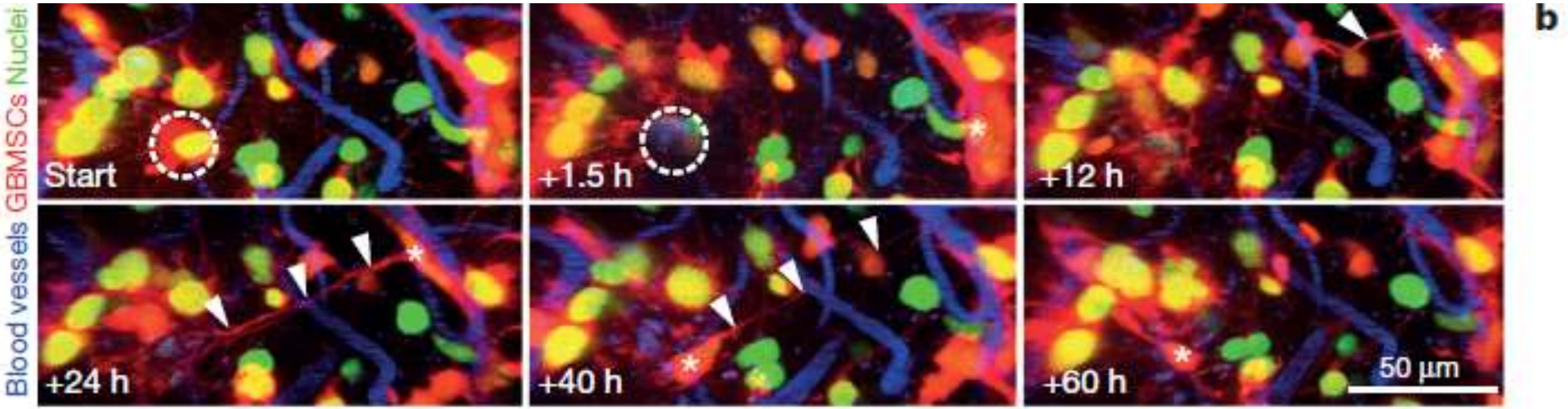
ARTICLE

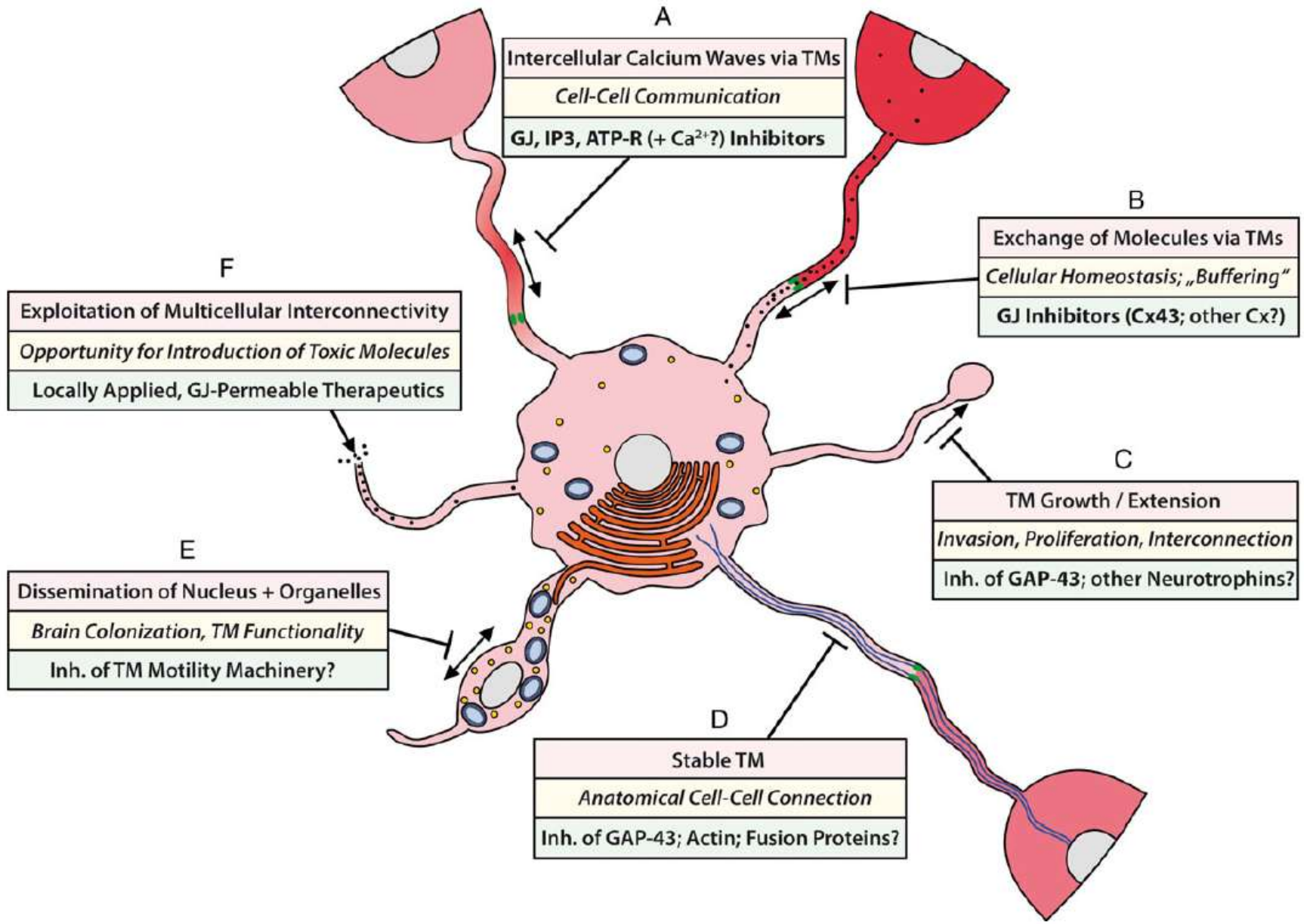
doi:10.1038/nature16071

Brain tumour cells interconnect to a functional and resistant network

Matthias Osswald[1,2], Erik Jung[1,2]*, Felix Sahm[3,4]*, Gergely Solecki[1,2]*, Varun Venkataramani[5], Jonas Blaes[1,2], Sophie Weil[1,2], Heinz Horstmann[5], Benedikt Wiestler[1,2,6], Mustafa Syed[1,2], Lulu Huang[1,2], Miriam Ratliff[2,7], Kianush Karimian Jazi[1,2], Felix T. Kurz[8], Torsten Schmenger[1,2], Dieter Lemke[1,2], Miriam Gömmel[1,2], Martin Pauli[9], Yunxiang Liao[1,2], Peter Häring[10], Stefan Pusch[3,4], Verena Herl[11], Christian Steinhäuser[11], Damir Krunic[12], Mostafa Jarahian[13], Hrvoje Miletic[14], Anna S. Berghoff[15], Oliver Griesbeck[16], Georgios Kalamakis[17], Olga Garaschuk[17], Matthias Preusser[18], Samuel Weiss[19,20,21], Haikun Liu[22], Sabine Heiland[8], Michael Platten[1,23], Peter E. Huber[24,25], Thomas Kuner[5], Andreas von Deimling[3,4], Wolfgang Wick[1,2] & Frank Winkler[1,2]

Role of **Tumour Microtubules** in treatment resistance:




A
Intercellular Calcium Waves via TMs
Cell-Cell Communication
GJ, IP3, ATP-R (+ Ca2+?) Inhibitors
B
Exchange of Molecules via TMs
Cellular Homeostasis; „Buffering"
GJ Inhibitors (Cx43; other Cx?)
C
TM Growth / Extension
Invasion, Proliferation, Interconnection
Inh. of GAP-43; other Neurotrophins?
D
Stable TM
Anatomical Cell-Cell Connection
Inh. of GAP-43; Actin; Fusion Proteins?
E
Dissemination of Nucleus + Organelles
Brain Colonization, TM Functionality
Inh. of TM Motility Machinery?
F
Exploitation of Multicellular Interconnectivity
Opportunity for Introduction of Toxic Molecules
Locally Applied, GJ-Permeable Therapeutics

THANK YOU.