Update on:
The WHO Classification of Pediatric Brain Tumors

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IAP Cologne, 28 Sept, 2016
Objectives

1. To be able to identify the common tumors of the CNS occurring in childhood and how our changing understanding of them is reflected in the most recent revision of the WHO classification of tumors of the nervous system.

2. To understand the biological underpinnings of why these tests were chosen to discriminate among these brain tumors.

3. To understand when to ask for and how to interpret the tests recommended to be used in evaluating brain tumors.
June 2015, WHO Committee on the Classification of Brain Tumors convened in Heidelberg, Germany for a three day meeting to incorporate the “significant advances” in biomarker identification that had been made in brain tumor classification.

Relied upon biomarker findings confirmed in at least 3 major studies.
Brain Tumors of Children

- **Gliomas**
  - Astrocytomas
  - Oligodendrogliomas
  - Ependymomas
- **Malignant Embryonal Tumors**
  - Medulloblastomas
  - Atypical Teratoid/Rhabdoid Tumors
  - Embryonal Tumor with Multilayered Rosettes
  - Neuroblastoma/Ganglioneuroblastoma
- **Neuronal and Mixed Neuronal-glial tumors**
- **Pineal parenchymal tumors**
Diffuse Astrocytic and Oligodendroglial Tumors

- **Diffuse Astrocytoma** (II)
- **High Grade Astrocytoma** (III-IV)
  - Anaplastic Astrocytoma
  - Glioblastoma
- **Diffuse midline glioma, H3-K27M mutant**
- **Oligodendroglioma** (II)
  - Anaplastic oligodendroglioma (III)
- **Oligoastrocytoma, NOS** (II)
  - Anaplastic oligoastrocytoma, NOS (III)
Other Astrocytic Tumors

- *Pilocytic astrocytoma (I)*
  - *Pilomyxoid astrocytoma (ungraded)*
- *Subependymal giant cell astrocytoma (I)*
- *Pleomorphic xanthoastrocytoma (II)*
  - *Anaplastic Pleomorphic Xanthoastrocytoma (III)*
Pediatric High Grade Astrocytoma

- Most commonly found in the cerebral hemispheres of adults, in children they occur in the midline
  - pons - thalamus
- Hydrocephalus
- Diffusely infiltrative
Midline glioma
Pediatric High Grade Astrocytoma
DNA is wrapped around histones which can be modified to regulate transcription. In order to prevent aberrant transcription, genomic repeats are packaged into a condensed chromatin structure which restricts accessibility to transcriptional machinery. Maintaining the architecture at these sites is critical to genome stability.
Pediatric High Grade Astrocytoma
WHO Grade III/IV

- Both midline and hemispheric tumors exhibit mutations in a histone protein, H3.3 or H3.1
  - K27M mutation in 78% of midline tumors
  - G34R/V mutation in 14% of cerebral hemispheres
    - More divergent histologic patterns with this mutation
H3 K27M mutations are found in 60-75% of midline gliomas in children.
Additional non-defining mutations in H3K27M gliomas

- TP53 mutation
- ATRX mutation
- CDKN2A/B homozygous deletion
- PDGFRa amplification
- CDK4/6 or CCND1-3 amplification
- MYC/PVT1 amplification
Infantile High Grade Astrocytoma

- In infants, high grade gliomas may also occur in the cerebral hemispheres.
- These tumors may demonstrate mutations in neurotropin receptor kinase (NTRK).
Pediatric Astrocytoma

- Diffuse astrocytoma, NOS
- *Pediatric High Grade Astrocytoma, H3 K27M-mutant*
- Pediatric High Grade Astrocytoma, NOS
- Pilocytic astrocytoma
- Pilomyxoid astrocytoma - ungraded
- Subependymal giant cell astrocytoma
- Pleomorphic xanthoastrocytoma, Grade II
- *Anaplastic pleomorphic xanthoastrocytoma, Grade III*
Oligodendroglioma

- Oligodendroglioma, NOS
  - Anaplastic oligodendroglioma, NOS
- Oligoastrocytoma, NOS
  - Anaplastic oligoastrocytoma, NOS
BRAF?

- BRAF:KIAA has been identified in a small subset of high grade gliomas and is not specific for pilocytic astrocytomomas.
- BRAFv600e has been identified in a small subset of high grade gliomas and is not specific for PXA or ganglioglioma.
Ependymoma
- Arise from the ependymal lining of the ventricular system or the remnants of the ependymal lining of the central canal within the spinal cord.

Ependymal rosettes mimic the ependymal lining of the ventricle.
Grading of ependymomas

- Mitotic index and foci of poorly differentiated tumor cells seem to correlate with prognosis.
- However, consensus on these features is poor and few studies rely upon histopathology to subdivide these tumors anymore.
- Molecular subtyping seems eminent.
C11orf95–REL A fusions drive oncogenic NF–κB signalling in ependymoma

- Demonstrated by a REL A break-apart FISH assay.
- Poor prognosis in posterior fossa ependymomas.
Post Fossa Ependymoma

- **Group A**
  - “Supratentorial”
  - Young
  - More aggressive
  - RELA fusion

- **Group B**
  - “spinal type”
  - Older
  - Less aggressive
Ependymoma

- Subependymoma
- Myxopapillary ependymoma
- Ependymoma
- Papillary ependymoma
- Clear cell ependymoma
- Tanycytic ependymoma
- Ependymoma, RELA fusion-positive
- Anaplastic ependymoma
Intrinsic Tumors of Childhood

- Embryonal
  - Medulloblastomas
    - Multiple variants
  - Atypical Teratoid/Rhabdoid Tumors
    - AT/RT (with BAF47 loss)
    - CNS embryonal tumor with rhabdoid features, NOS
  - PNETs – renamed “Embryonal Tumor”
  - Cerebral Neuroblastoma or Ganglioneuroblastoma

Duke Pathology
Medulloblastoma

- **Molecular subtyping is endorsed as primary factor**
- **Morphologic subtyping is retained in cases for which molecular subtyping is not available**
Medulloblastomas

Classic

Nodular
Nodular/Desmoplastic Medulloblastoma
Medulloblastoma with Extensive Nodularity (MBEN)
Large Cell/ Anaplastic Medulloblastoma
Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas

Marcel Kool · Andrey Korshunov · Marc Remke · David T. W. Jones · Maria Schlanstein · Paul A. Northcott · Yoon-Jae Cho · Jan Koster · Antoinette Schouten-van Meeteren · Dannis van Vuurden · Steven C. Clifford · Torsten Pietsch · Andre O. von Bueren · Stefan Rutkowski · Martin McCabe · V. Peter Collins · Magnus L. Bäcklund · Christine Haberler · Franck Bourdeaut · Olivier Delattre · Francois Doz · David W. Ellison · Richard J. Gilbertson · Scott L. Pomeroy · Michael D. Taylor · Peter Lichter · Stefan M. Pfister
Classification of medulloblastoma

- Four molecular groups with different profiles of clinical utility
  - WNT
  - SHH
  - SHH with TP53 mutation
  - Group 3/4
- Classic tumor plus variants with clinicopathologic utility
  - Desmoplastic / nodular medulloblastoma
  - Medulloblastoma with extensive nodularity
  - Large cell / anaplastic (LC/A) medulloblastoma
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<td>Non-WNT/SHH</td>
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Embryonal Tumors

Medulloblastoma, genetically defined
  Medulloblastoma, WNT activated
  Medulloblastoma, SHH activated, \(TP53\) mutated
  Medulloblastoma, SHH activated, \(TP53\) wild-type
  Medulloblastoma, non-WNT/non-SHH
    *Medulloblastoma, group 3*
    *Medulloblastoma, group 4*

Medulloblastoma, histologically defined
  Medulloblastoma, classic
  Medulloblastoma, desmoplastic/nodular
  Medulloblastoma with extensive nodularity
  Medulloblastoma, large cell/anaplastic

*Medulloblastoma, NOS*
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Atypical Teratoid/Rhabdoid Tumor (AT/RT)

- Found to lack a chromatin remodeling complex that functioned as a tumor suppressor gene (INI1).
- INI1 complex lacked BAF47 or, more rarely, BRG1.
Chromatin remodeling

Gene “switched on”
- Active (open) chromatin
- Unmethylated cytosines (white circles)
- Acetylated histones

Gene “switched off”
- Silent (condensed) chromatin
- Methylated cytosines (red circles)
- Deacetylated histones

Transcription possible

Transcription impeded
AT/RT
Intrinsic Tumors of Childhood

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    - CNS embryonal tumor with rhabdoid features, NOS
  - PNETs – renamed “Embryonal Tumor”
    - Embryonal tumour with multilayered rosettes, C19MC altered
  - Cerebral Neuroblastoma or Ganglioneuroblastoma
Embryonal tumour with multilayered rosettes, C19MC altered

- “Ependymoblastoma”
- “Medulloepithelioma”
- “Embryonal Tumor with Abundant Neuropil and True Rosettes”
CNS-PNETs with C19MC amplification and/or LIN28 expression comprise a distinct histogenetic diagnostic and therapeutic entity

Tara Spence · Patrick Sin-Chan · Daniel Picard · Mark Barszczyn · Katharina Hoss · Mei Lu · Seung-Ki Kim · Young-Shin Ra · Hideo Nakamura · Jason Fungusaro · Eugene Hwang · Erin Kiehna · Helen Toledano · Yin Wang · Qing Shi · Donna Johnston · Jean Michaud · Milena La Spina · Anna Maria Buccoliero · Dariusz Adamek · Sandra Camelo-Piragua · V. Peter Collins · Chris Jones · Nabil Kabbara · Nawaf Jurdi · Pascale Varlet · Arie Perry · David Scharnhorst · Xing Fan · Karin M. Muraszko · Charles G. Eberhart · Ho-Keung Ng · Sridharan Gururangan · Timothy Van Meter · Marc Remke · Lucie Lafay-Cousin · Jennifer A. Chan · Nongnuch Sirachainan · Scott L. Pomeroy · Steven C. Clifford · Amar Gajjar · Mary Shago · William Halliday · Michael D. Taylor · Richard Grundy · Ching C. Lau · Joanna Phillips · Eric Bouffet · Peter B. Dirks · Cynthia E. Hawkins · Annie Huang
Embryonal tumour with multilayered rosettes, C19MC altered

Frequent amplification of a chr19q13.41 microRNA polycistron (C19MC) in aggressive primitive neuro-ectodermal brain tumors

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Embryonal Tumors of Childhood

- Medulloblastomas
  - Multiple variants
- AT/RT (with BAF47 or BRG1 loss)
- Embryonal Tumor with Rhabdoid Features, NOS
- Embryonal tumor with multilayered rosettes, C19MC altered
- Embryonal tumor with multilayered rosettes, NOS
- Medulloepithelioma
- CNS neuroblastoma
- CNS ganglioneuroblastoma
- CNS Embryonal Tumor, NOS (formerly “PNET”)
Neuronal and Mixed Neuronal-glial tumors

- **Diffuse leptomeningeal glioneuronal tumor**
- Dysembryoplastic neuroepithelial tumor
- Gangliocytoma
- Ganglioglioma
- Anaplastic ganglioglioma
- Dysplastic cerebellar gangliocytoma
- Desmoplastic infantile astrocytoma and ganglioglioma
- Papillary glioneuronal tumor
- Rosette-forming glioneuronal tumor
- Central neurocytoma
- Extraventricular neurocytoma
- Cerebellar liponeurocytoma
- Paraganglioma
Pineal parenchymal tumors

- Pineocytoma
- Pineal parenchymal tumor of intermediate differentiation
- Pineoblastoma
- Papillary tumor of the pineal region
Objectives

1. To be able to identify the common tumors of the CNS occurring in childhood and how our changing understanding of them is reflected in the most recent revision of the WHO classification of tumors of the nervous system.

2. To understand the biological underpinnings of the most common tests used in diagnostic neuropathology

3. To understand when to ask for and how to interpret the most common molecular tests used in evaluating brain tumors.
QUESTIONS?