PRACTICAL USE OF MOLECULAR MARKERS IN DIAGNOSTIC NEUROPATHOLOGY

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THE PREMISE
• A PHENOTYPE CAN BE ASSOCIATED WITH MULTIPLE GENOTYPES AND VICE VERSA
• THE APPROACH TO THE USE OF MOLECULAR MARKERS SHOULD BE BASED ON A MORPHOLOGICALLY AND CLINICALLY SOUND ALGORITHM

ALGORITHM

- Is it normal or abnormal?
- Is it neoplastic or non-neoplastic?
- Is it benign or malignant?
- Is it glial or non-glial?
- What kind of glial tumor?

CLINICAL DATA

CLINICAL DATA

RADIOLOGICAL DATA

DX
OUTLINE

• SMALL BIOPSY: GLIOSIS OR GLIOMA
• IF IT IS A GLIOMA, DO I NEED ANYTHING OTHER THAN H&E?
• POSTERIOR FOSSA TUMORS IN CHILDREN

THIS LOOKS LIKE A GLIOMA BUT COULD IT BE GLIOSIS
GLIAL MARKERS
- GFAP
- Olig-2
- VIM
- S-100
- EMA
- D2-40
- NSE

TUMOR MARKERS
- MIB-1
- P53
- IDH-1 (R132H)
- ATRX
- WT-1
- 1p19q, EGFR, PTEN, (FISH)
- MGMT, TERT PROMOTER (PCR)

IDH Gene Mutation
Metabolic Reprogramming: A Cancer Hallmark Even Warburg Did Not Anticipate
PS. Ward, CB. Thompson
CANCER Cell vol 21 no (2012)
IDH STORY

- Useful for diagnosis: YES
- Useful for prognosis: YES
- Predictive for treatment decisions: NO

COURTESY OF DR. MELIKE PEKMEZCI, UCSF
ATRX STORY

- Useful for diagnosis: YES
- Useful for prognosis: NO
- Predictive for treatment decisions: NO
1P19Q STORY

- Useful for diagnosis: YES
- Useful for prognosis: YES
- Predictive for treatment decisions: YES?

MGMT STORY

- Useful for diagnosis: NO
- Useful for prognosis: NO
- Predictive for treatment decisions: YES?

What we now know about adult glioblastoma
5 distinct genetic/epigenetic/transcriptional subtypes of adult GBM

A CHILD WITH A POSTERIOR FOSSA TUMOR

- abnormal
- neoplastic
- low grade or benign
- glial
- type?
MIB-1 (Ki-67)

GFAP

OLIG-2

pERK

P16
FISH analysis for KIAA1549-BRAF shows duplication
IHC suggests downstream pERK activation

PILOCYTIC AND PILOMYXOID ASTROCYTOMA

A CHILD WITH A POSTERIOR FOSSA TUMOR

- abnormal
- neoplastic
- malignant
- non-glial...well NOT SURE
MEDULLOBLASTOMA GENETICS

- **GROUP A**: Wnt Pathway APC, Wnt, β-catenin mutations, classical histology
  - TURCOT Syndrome, APC mutations
  - β-catenin

- **GROUP B**: SHH Pathway PTCH, SHH, SMOH mutations (nodular/desmoplastic variant)
  - GAB-1
  - GORLIN Syndrome, germline PTCH mutations

- Isochromosome 17q in 40% of classic type

- MYC-C & MYC-N amplifications: poor prognosis
  - (preferentially in the anaplastic/large cell variant)

REMEMBER

- **ONE GENOTYPE – ONE PHENOTYPE IS A MYTH, AND A GROSS UNDERESTIMATION OF BIOLOGY**
- **STARTING POINT IS MORPHOLOGY (TODAY)**
- **YOU CAN NO LONGER IGNORE MOLECULAR PATHOLOGY AND KEEP YOUR HEAD IN H&E**

THANK YOU!!!!