**Pediatric Central Nervous System (CNS) Tumors, 2021 ASPHO Board Review Course**

**Practice Test Questions**

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**\*Of note, questions #1, #6, #10, #14, #15, #16, #17, #18, #19 and 20 are modified or completely new from 2019 Course**

1. A 9-year-old boy presents to the emergency department with emesis and headache of 3 weeks’ duration. MRI reveals a large heterogeneous mass in the cerebellum. He undergoes a resection, and the pathology is most consistent with a classic medulloblastoma.

Which of the following findings would classify the patient as a high-risk medulloblastoma?

A. Elevated serum and CSF AFP and beta-HCG tumor markers

B. WNT subgrouping on molecular classification

C. A presurgical spine MRI that reveals bulky tumor in the spine

D. A postoperative brain MRI with no signs of residual tumor

**Explanation**

Although molecular classification is slowly becoming part of prognostication and treatment paradigms for medulloblastoma, the most accepted and studied risk groups are standard- and high-risk medulloblastoma. WNT subgrouping seems to portend an improved survival, and by itself does not make a patient high-risk. In addition to histology (classic, desmoplastic, extremely nodular, and anaplastic/large cell), the other characteristics that define risk groups are age, amount of residual disease, and metastases. Both lumbar CSF cytology and a full spine MRI are necessary to evaluate for metastatic disease. Spinal MRI should be done preoperatively or 10 to 14 days postoperatively to avoid postoperative changes that can make interpretation difficult. Lumbar CSF cytology also should be done 10 to 14 days postoperatively. Metastatic disease in the spine would increase the patient’s risk level to high and change treatment. Medulloblastoma metastases typically are confined to the brain and spine. Medulloblastoma does not secrete tumor markers.

2. A 20-month-old girl presents with persistent emesis and increased sleepiness. Brain MRI reveals a cerebellar mass and associated hydrocephalus. She undergoes a complete resection of the mass. While awaiting the final pathology, the parents ask about high-dose chemotherapy and autologous hematopoietic stem cell rescue treatment approaches.

For which of the following diagnoses would this treatment be the most widely accepted and successful strategy for this child?

A. Low-grade glioma

B. Choroid plexus papilloma

C. Ependymoma

D. Medulloblastoma

**Explanation**

The use of high-dose chemotherapy and autologous hematopoietic cell rescue has been tested in many infant brain tumors in an effort to reduce, delay, or avoid radiotherapy, given the late effects associated with craniospinal radiation and the developing infant brain (ie, neurocognitive dysfunction, ototoxicity, endocrine dysfunction, secondary malignancy). Medulloblastoma is among the diagnoses listed as having the most evidence and success with this approach. Most practitioners would use this approach for a child younger than 3 years with a diagnosis of medulloblastoma. Although this approach has been tested in ependymoma, it is not universally accepted, and most practitioners would treat a 20-month-old with a posterior fossa ependymoma with a resection followed by focal radiotherapy. In fact, most current studies use focal radiation of the posterior fossa down to age 12 months for children with ependymoma. Neither choroid plexus papilloma nor low-grade glioma is treated with this approach.

3. A 11-year-old girl presents with ataxia, headaches and emesis that has worsened over the last several weeks. CT in the emergency department reveals a large mass in the cerebellum with associated hydrocephalus. After she is stabilized, the patient undergoes a complete resection of the mass that preliminarily is most consistent with a classic medulloblastoma. Molecular testing has been sent, but the results are not yet available.

Which of the following molecular aberrations would be most consistent with a medulloblastoma with excellent survival?

A. Wingless (WNT) pathway abnormality

B. Loss-of-function alterations in neurofibromin 1

C. BRAFv600e mutation

D. Tuberous sclerosis complex-1 (TSC-1) abnormality

E. Group 3 medulloblastoma

**Explanation**

Although classifications are constantly evolving as new molecular insights are obtained, the most accepted subgrouping of medulloblastoma is into four broad molecular subgroups: WNT, SHH, Group 3, and Group 4. The WNT subgroup is the rarest and typically occurs in children between 10 and 12 years old, has a classic histology, and, based on historic data and developing prospective data, has excellent survival outcomes (more than 95% in most series). Loss-of-function alterations in neurofibromin 1 are associated with a diagnosis of neurofibromatosis type 1 and low-grade glioma development. BRAFv600e aberrations, such as BRAF V600E mutation and the BRAF KIAA-1549 fusion, are common in pilocytic astrocytomas, the most common low-grade glioma in children. TSC-1 abnormality is seen in children with tuberous sclerosis who have an increased risk of developing subependymal giant cell astrocytomas. Although Group 3 is a subgroup of medulloblastoma, it typically has a very poor outcome.

4. A 22-month-old girl presents with 6 months of failure to thrive despite eating normally. She currently is at less than 3% for weight on the growth curve, and 8 months ago she was at the 50%. She has had an extensive GI, endocrinological, and genetic evaluation, but no etiology has been identified. Over the last week, she has developed new persistent emesis. MRI of her brain reveals a large mass in the hypothalamus with associated hydrocephalus. A third ventriculostomy and biopsy are performed.

This history is most consistent with what pathologic diagnosis?

A. Ependymoma

B. Low-grade glioma

C. Medulloblastoma

D. Thalamic cyst

**Explanation**

This vignette is a classic case of Diencephalic Syndrome. This syndrome most commonly is seen in infants and young children. It is characterized by failure to thrive and severe emaciation despite normal or only slightly decreased intake. It also sometimes presents with hyperactivity and euphoria. It can go undiagnosed for many months because typically it does not initially present with the classic findings of obstructive hydrocephalus such as headaches and emesis. Although other histologies have been described, it is most commonly caused by a low-grade glioma such as a pilocytic astrocytoma in the hypothalamic region. A complete and thorough understanding of the pathophysiology of these associated symptoms has not been achieved. Typically these patients are treated with low-grade glioma chemotherapy such as carboplatin/vincristine. Most commonly the failure to thrive improves with treatment. It should be noted that this is a very rare cause of failure to thrive, but if all other etiologies have been eliminated, one should at least consider brain imaging.

5. A 6-year-old boy presents with a 6-month history of “clumsiness.” Initially his family thought it was due to him needing glasses, but it has persisted and slightly worsened over the last month despite a new eyeglass prescription. Over the last 2 days he has complained of headaches and developed some right-handed weakness. Outpatient MRI of his brain reveals a mass in the left frontal-parietal region of the brain with very mild associated hydrocephalus. He undergoes a resection of the mass that is consistent with a pilocytic astrocytoma. Postoperative imaging reveals a gross total resection without any evidence of residual disease.

If this patient’s tumor is sent for molecular testing, which of the following is the most likely abnormality to be found?

A. Aberrations in the MAPK pathway such as a BRAFKIAA1549 fusion

B. Sonic Hedgehog (SHH) abnormalities

C. Tuberous sclerosis complex-2 (TSC-2) abnormality

D. TP53 mutation

**Explanation**

Over the last decade, it has become understood that the most common molecular abnormalities in pediatric low-grade glioma are abnormalities of the MAPK pathway. The most common specific abnormality is the BRAFKIAA1549 fusion, which is estimated to be present in 60-80% of all pilocytic astrocytomas. For children with a completely resected low-grade glioma (LGG) such as pilocytic astrocytoma, the most accepted treatment paradigm is observation alone because both progression-free and overall survival after a gross total resection are excellent (greater than 90%). For children with LGG and residual disease after surgery or associated symptoms such as vision dysfunction (as seen in optic pathway LGG), the usual first-line treatment is LGG chemotherapy alone. SHH is associated with medulloblastoma; TSC-2 is associated with tuberous sclerosis and subependymal giant cell astrocytomas and dysregulates the mTOR pathway. In fact, if resection is not feasible or safe, a first-line therapy is the use of mTOR inhibition, which has been very effective. In CNS tumors, TP53 abnormalities are most commonly seen in high-grade gliomas and medulloblastomas. Germline mutations of TP53 are seen in Li-Fraumeni, a tumor predisposition syndrome.

6. A 6-year-old boy is noted to have worsening visual acuity on serial eye exams. Recent MRI of his brain and orbits reveals an optic chiasm mass, most consistent with an optic pathway glioma. Upon further examination, the physician notes axillary freckling and numerous “spots” on the patient’s skin.

This patient most likely has a which of the following genetic disorders?

A. Neurofibromatosis type-1 (NF1)

B. Li Fraumeni syndrome

C. Tuberous sclerosis

D. Cystic Fibrosis

**Explanation**

Children with neurofibromatosis type-1 (NF-1) have about a 15% to 20% risk of developing low-grade gliomas (LGG), most commonly in the optic pathway. They also have a variety of other abnormalities such as axillary freckling and café-au-lait spots. Li Fraumeni syndrome is associated with p53 mutations and high-grade tumors, like high-grade gliomas and sarcomas. The characteristic brain tumor in tuberous sclerosis is a subependymal giant cell astrocytoma (SEGA). Patients with cystic fibrosis are not at increased risk of CNS tumors. LGGs in patients with NF1 are often indolent and do not necessitate any therapy at all. However, most would agree that when visual acuity is affected by the tumor, treatment is indicated to prevent further vision decline and possibly improve vision in some patients. The best known current therapy is LGG chemotherapy. Common first-line LGG chemotherapies are combinations of carboplatin/vincristine, vinblastine alone, or a combination of thioguanine, procarbazine, lomustine (CCNU), and vincristine (TPCV). TPCV often is avoided for patients with NF-1 because of the risks of secondary malignancy with alkylator use. Radiotherapy is avoided for children with NF-1 because of the high risk of secondary malignancy.

7. A 14-year-old boy presents with a 2-week history of worsening headaches and left-sided weakness. MRI reveals a 2-cm × 2-cm mass in the right cerebrum with associated mild midline shift. A complete resection is performed, and the pathology is consistent with a World Health Organization grade IV high-grade glioma (HGG).

Which of the following is the most likely survival outcome for a 14-year-old patient with HGG treated with a combination of focal radiotherapy and HGG chemotherapy?

A. 5-year overall survival of 50%

B. 5-year overall survival of 90%

C. No survivals have been reported

D. 5-year survival of 15% to 20%

**Explanation**

The survival rates for children with HGG are dismal, with most prospective and historic reports showing 15% to 20% overall survival at 5 years. However, there are some survivors, but we are only just beginning to understand the molecular features that distinguish those patients who survive from those who do not.

8. A 14-year-old boy presents with a 2-week history of worsening headaches and left-sided weakness. MRI reveals a 2-cm × 2-cm mass in the right cerebrum with associated mild midline shift. A complete resection is performed, and the pathology is consistent with a World Health Organization grade IV high-grade glioma (HGG). After meeting with the patient’s family, you discover that his maternal uncle died of a “brain tumor” at age 40, his maternal first cousin developed an undifferentiated sarcoma in her 20s, and his mother was just diagnosed with an adrenocortical carcinoma.

Which of the following molecular findings would be most consistent with this family’s history?

A. A germline mutation in TP53

B. Loss-of-function alterations in neurofibromin 1

C. Mutations in the NF-2 gene

D. No molecular abnormality

**Explanation**

This family history, with multiple high-grade tumors (adrenocortical carcinoma, high-grade glioma and sarcomas), is most consistent with a diagnosis of Li-Fraumeni syndrome, a cancer predisposition syndrome characterized by a germline mutation in TP53, a tumor suppressor gene. Loss-of-function alterations in neurofibromin 1 are seen in patients with NF-1 and are associated with low-grade glioma. Mutations in NF-2 are associated with a diagnosis of neurofibromatosis type 2, and these patients are at risk for developing acoustic schwannomas and ependymomas. It would be much less likely to *not* find a molecular abnormality in a history this strong for cancers, especially in young patients.

9. A 6-year-old boy presents with emesis for 3 weeks and new ataxia over the last 2 days. MRI reveals a large cerebellar mass with associated hydrocephalus. He undergoes a tumor resection, and the pathology is most consistent with an ependymoma. Post-operative imaging reveals **no** residual disease, and there are no signs of metastases on spine MRI or lumbar CSF cytology.

What is the most accepted post-operative treatment approach?

A. Focal radiotherapy

B. High-dose chemotherapy with hematopoietic cell rescue

C. Craniospinal radiation followed by 6 months of dose-intense chemotherapy

D. Intrathecal chemotherapy

**Explanation**

The best known treatment for ependymoma is a gross total resection followed by focal radiotherapy. Some practitioners may use a radiation-delaying approach in very young children, but in a 6-year-old, focal radiotherapy is the most widely accepted post-surgical treatment approach with the best-reported outcomes among the answer choices listed.

10. An 8-year-old boy undergoes a resection of a tumor in the right cerebrum next to the lateral ventricle (supratentorial). The pathologist feels the histology is most consistent with an ependymoma. The tumor is sent for advanced molecular and genetic testing. Which of the following findings would further support a diagnosis of ependymoma?

1. BRAFKIAA1549 fusion
2. BRAFV600E mutation
3. RELA fusion
4. H3K27M mutation

**Explanation**

Both A and B (the BRAF abnormalities) are most commonly seen in glial tumors, specifically in low-grade glioma. BRAFKIAA1549 fusion is seen in 60% to 80% of classic pilocytic astrocytoma, the most common pediatric low-grade glioma. The BRAFV600E mutation is most commonly seen in low-grade glioma but has also been described in about 8% to 10% of high-grade glioma. Supratentorial ependymomas seemingly are divided by two major molecular aberrations, including the C11orf95-RELA fusion and the YAP1 fusion. The RELA fusion is much more common and seems to portend a worse prognosis, whereas the YAP1 fusion is quite rare and most often seen in infants with an improved survival outcome. The H3K27M mutation is a defining characteristic of diffuse midline gliomas, such as diffuse intrinsic pontine glioma (DIPG).

11. A 14-year-old boy is admitted to the hospital with a 3-month history of increased thirst and urination. Laboratory results evaluating his serum and urine reveal a diagnosis consistent with diabetes insipidus (DI). He initiates treatment with desmopressin with subsequent improvement. Over the next several months, however, he develops worsening headaches and emesis. MRI of his brain reveals 2 distinct masses with associated obstructive hydrocephalus, one in the suprasellar region and one in the pineal region.

Which of the following is the most likely histologic diagnosis?

A. Metastatic medulloblastoma

B. Metastatic ependymoma

C. Langerhans cell histiocytosis (LCH)

D. Bifocal CNS germ cell tumor (GCT)

**Explanation**

This prolonged history with endocrine symptoms (DI) is a common finding in patients with CNS GCTs in the suprasellar/pituitary region. The concomitant presence of a mass in the pineal region is known as a bifocal or doublet lesion. This constellation of findings is most consistent with a CNS GCT, probably a germinoma. Medulloblastoma is defined by its presence in the cerebellum, and therefore, the locations of his masses exclude option A. It would be very unusual to have a metastatic ependymoma with this distinct pattern on MRI, especially when the patient presents with DI. Finally, although LCH can present with DI, the presence of a concomitant pineal mass makes this option very unlikely.

12. A 3-month-old boy presents with rapidly increasing head circumference noted by his pediatrician. Imaging reveals a large mass in the cerebellum. The infant is also noted to have mild hematuria, and a renal ultrasound is performed revealing a large left-sided renal mass.

Which of the following abnormalities is most consistent with this pattern of findings?

A. BRAFv600e mutation in the tumors

B. Diagnosis of neurofibromatosis type 1 (NF-1)

C. Diagnosis of neurofibromatosis type 2 (NF-2)

D. Germline mutation in SMARCB1/INI-1

**Explanation**

This scenario is most consistent with an atypical teratoid rhabdoid tumor (AT/RT) in the brain. The presentation before age 12 months and the concomitant renal mass are most suggestive of a germline mutation. AT/RT and malignant rhabdoid tumors are characterized by abnormalities in SMARCB1/INI-1, which often are pathognomonic. Germline mutations in SMARCB1/INI-1 predispose patients and families to rhabdoid tumors and schwannomatosis. BRAFv600e is most commonly seen in low-grade glioma (LGG) in children. NF-1 predisposes to LGG, especially of the optic pathway. NF-2 predisposes to acoustic schwannomas and ependymomas.

13. A 5-year-old boy presents with a 3-week history of his right eye “not moving to the right side.” The remainder of his neurologic exam is normal with the exception of a weak gag. MRI of the brain reveals a diffusely infiltrative mass in the pons.

If treated with focal radiotherapy, what is the expected survival outcome for this patient?

A. Most children succumb to this disease within 10 to 12 months of diagnosis.

B. 5-year overall survival is approximately 50%.

C. 5-year overall survival is close to 95%.

D. A prognosis cannot be made without a tissue diagnosis.

**Explanation**

This child has a diffuse intrinsic pontine glioma (DIPG). These patients commonly present with a short duration of cranial nerve findings (such as weak gag, lateral rectus palsy, and hoarse voice). Characteristic imaging typically reveals a large, diffuse infiltrative mass with its epicenter in the pons. Although tissue biopsy for molecular testing has become more common, it is still not required for a diagnosis. The diagnosis can be made by MRI alone, and there is a median survival of 10 to 12 months in most series.

14. A 5-year-old boy presents with a 3-week history of his right eye “not moving to the right side.” The remainder of his neurologic exam is normal with the exception of a weak gag. MRI of the brain reveals a diffusely infiltrative mass in the pons.

If this patient were to undergo a stereotactic biopsy, what would be the most likely molecular finding?

1. BRAFKIAA1549 fusion
2. Trisomy 21
3. H3 K27M mutation
4. RELA fusion

**Explanation**

Advances over the last decade have revealed a characteristic histone mutation in DIPG and other midline high-grade gliomas in H3 K27M. The World Health Organization now classifies midline tumors harboring this abnormality as diffuse midline gliomas (DMG), which portend a worse prognosis than other high-grade gliomas. BRAFKIAA1549 fusion is commonly seen in low-grade glioma. Trisomy 21 is not commonly seen in brain tumors. RELA fusion is a common finding in supratentorial ependymoma.

15. A 25-year-old woman was treated with craniospinal radiation when she was of 5 years old for a high-risk medulloblastoma. She presents in long-term follow-up clinic. Which of the following is most likely to be a direct result of her exposure to craniospinal radiation?

1. No late effects
2. Hypertension
3. Hypothyroidism
4. Complete blindness

**Explanation**

Receiving craniospinal radiation as a child is associated with numerous late effects, including neurocognitive delay/decline, hearing deficits, endocrine abnormalities (such as hypothyroidism), and risk of developing a secondary malignancy (usually a high-grade glioma or meningioma 8 to 10 years after treatment). Complete blindness and hypertension without other predisposing factors are not common direct side effects of craniospinal radiation. It would be exceedingly rare that a child who received radiation therapy at such a young age would have no late effects.

16. You are seeing a new patient in a brain tumor consult with a resident. The only information you know is that the child is 5 years old and presented with headaches and emesis. The resident asks you what histology is the most common brain tumor encountered in children of all ages (0-18 years old). What is the best answer?

1. Atypical teratoid/rhabdoid tumor (AT/RT)
2. Ependymoma
3. Choroid plexus carcinoma
4. Astrocytoma

**Explanation**

Astrocytoma is the most common CNS tumor of childhood, representing 40% to 50% of all CNS tumors. They are most commonly low grade (WHO grade I and II). Medulloblastoma is the second most common (the most common “malignant” brain tumor), and ependymoma is the third most common.

17. You are seeing a new patient in a brain tumor consult with a resident. The only information you know is that the child is 5 years old and presented with headaches and emesis. An MRI revealed a mass in the cerebellum. The resident asks you about common diagnoses seen in this location. Which of the following diagnoses would be present in the cerebellum?

1. Medulloblastoma
2. Optic nerve tumor
3. Diffuse intrinsic pontine glioma
4. Craniopharyngioma

**Explanation**

Although historic definitions have varied, the current understanding of medulloblastoma is a tumor located specifically in the cerebellum. Optic nerve tumors (most commonly low grade and often associated with NF1) occur in the optic nerves, as the name suggests. Diffuse intrinsic pontine gliomas (DIPG) occur specifically in the pons of the brainstem. Craniopharyngioma are most commonly seen in the supratentorium within the suprasellar and pituitary region.

18. Which of the following characteristics puts a child at the highest risk for developing a brain tumor?

A. A history of seizures

B. A history of recent trauma

C. A diagnosis of Li Fraumeni Syndrome

D. Presence of a ventricular-peritoneal (VP) shunt

**Explanation**

Of the items listed, only a known genetic predisposition syndrome, like Li Fraumeni, increases a child’s risk of developing a brain tumor. Li Fraumeni is a germline abnormality in TP53 and leads to numerous cancers at younger ages (breast, sarcoma, adrenal cortical carcinoma, and brain tumors). Another known association with brain tumor development/risk is a history of ionizing radiation.

19. A 7-year-old boy presents with increased stumbling and left-side weakness. An MRI reveals a large mass in the right thalamus. The pathologist tells you it appears to be a very aggressive glial tumor with high MIB index and numerous mitoses, most consistent with a high-grade glioma based upon initial morphology and histology. Molecular testing reveals an H3 K27M mutation. What is the diagnosis?

1. Medulloblastoma
2. Pilocytic astrocytoma
3. Diffuse midline glioma
4. Craniopharyngioma

**Explanation**

A high-grade glioma located in the midline and with the H3 K27M mutation defines the tumor as a diffuse midline glioma, according to WHO. Pilocytic astrocytoma can be located in the midline, but it would be very rare to have an H3 K27 mutation. Also, the histology of pilocytic astrocytoma is low grade. Medulloblastoma by definition is located in the cerebellum. Craniopharyngioma typically has a low-grade appearance and is most commonly located in the suprasellar and pituitary region.

20. In which of the following patients is craniospinal radiation currently part of standard therapy?

A. A 12-year-old girl with medulloblastoma that has spread to the spine on MRI

B. A 3-year-old boy with NF1-associated optic pathway tumor and no visual and no neurologic deficits on exam

C. A 7-year-old girl with a newly diagnosed pilocytic astrocytoma (a low-grade glioma) of the cerebellum who undergoes a gross total resection as seen on postoperative MRI

D. A 4-year-old boy with NF1-associated optic pathway tumor whose vision has declined significantly over the last several months.

**Explanation**

Craniospinal radiation is currently standard of care for children with high-risk medulloblastoma. (This case is high-risk due to metastases.) Radiation should be avoided at all costs in children with NF1 due to the high risk of secondary malignancy. The patient in option B may not require any treatment as patients with NF1-associated tumors are often not treated if the tumor is not causing functional deficits (vision loss, for example). The patient in option D may require therapy based on vision loss; however, first-line therapy for NF1-associated tumors is chemotherapy. Pilocytic astrocytoma that is completely resected is observed with surveillance imaging alone.