Acknowledgements

Sachin Jogal, M.D. Oncology
Julie Bender, PA Oncology
Mia Kelly, BA Illustrations
Medical College of Wisconsin
Children’ Hospital of Wisconsin
Saurabh Guleria M.D. Radiology
University of Alabama School of Medicine

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The goal of this presentation is to review common intracranial CNS complications in children with oncologic diseases.

Imaging is essential to look for reversible causes of acute neurological symptoms so that appropriate treatment can be given to minimize morbidity and mortality.
Background

Cancer is a devastating diagnosis for anyone, but particularly for children who have so much of life left ahead of them.

As survival rates for children with cancer in the U.S. continue to improve, detection of both short term and long term complications in children with oncologic disease has become more of an issue.
Background

“At least 70% of pediatric cancer survivors will develop at least one medical complication or disability by 30 years from diagnosis, most of which can be attributed to their previous cancer treatments.”

Wassim C. et al Endocrine-Related Cancer (2010) 17 R141-R159
Neurological complications in children with cancer can arise:

- A. from the cancer itself
- B. secondary to metastases
- C. or as a result of treatment
  - Surgery
  - Chemotherapy
  - Radiation therapy
  - Bone marrow transplantation
  - Steroids
Check list

The number of possible complications that can arise can seem formidable, so a checklist may simplify the way we screen for potential intracranial CNS complications:

1. Mass effect
2. Vascular compromise
3. Infection
4. Post therapy effects
5. CNS Metastasis or Secondary Neoplasms
6. Endocrine complications
1. Mass effect can cause:

- Hydrocephalus
- Midline shift
- Tonsillar herniation
- Perilesional edema
Hydrocephalus

A 10-month-old presented with lethargy, abnormal behavior, emesis and poor feeding.

Mass effect from a pineal anlage tumor resulted in hydrocephalus requiring EVD (external ventricular drainage) placement.
Tonsillar herniation

3 yo boy with medulloblastoma
2. Vascular complications

- A. Hemorrhage
- B. Dural venous sinus thrombosis
- C. Infarction
- D. PRES (posterior reversible encephalopathy)
- E. Cavernous angioma/microhemorrhage
A. Hemorrhage

Acute intracranial hemorrhage can result from cancer and cancer therapy with increasing risk when the platelet count is less than 10,000/mm³, if the patient is anticoagulated or when drugs such as prednisone and asparaginase are administered.

Vasquez et al Radiographics 2011;21:1123-1139
A. Hemorrhage

In this case a 10 year old suddenly became lethargic and difficult to arouse. At 15 months of age she underwent subtotal resection of a hypothalamic tumor and was treated with chemotherapy.

Spontaneous hemorrhage is seen in the tumor resection cavity.
B. Dural venous sinus thrombosis

This is a serious condition that can be caused by:

- Hyperleukocytosis
- Asparaginase and corticosteroids
- Dehydration shock
- Infection sepsis
- Tumor lysis syndrome
- Previous intracranial tumor resection
B. Dural venous sinus thrombosis

- For the diagnosis of venous thrombosis, MRI and MR venography are preferred. Whereas on unenhanced CT the thrombus is easily recognizable in the subacute phase as hyperattenuating lines, it can be mistaken for flowing blood in the acute phase, but MR venography will demonstrate absence of flow in either phase. Contrast enhanced CT will show a filling defect termed the “empty delta” sign.

Vasquez et al Radiographics 2011;21:1123-1139
Hyperleukocytosis is of great concern because it can cause leukostasis (symptomatic hyperleukocytosis), a medical emergency seen in children with AML who are in blast crisis. Blood vessel occlusion can then lead to dural venous sinus thrombosis.

“Prompt treatment is indicated since, if left untreated, the one-week mortality rate is approximately 20 to 40 percent.”

Charles A. Schiffer, MD, UpToDate, through March 2013
Hyperleukocytosis

- “Hyperleukocytosis refers to a laboratory abnormality that has been variably defined as a total leukemia blood cell count greater than $50 \times 10^9/L$ (50,000/microL) or $100 \times 10^9/L$ (100,000/microL).”

- In contrast, leukostasis (also called symptomatic hyperleukocytosis) is a medical emergency most commonly seen in patients with acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) in blast crisis.”

Charles A. Schiffer, MD, UpToDate, through March 2013
Noncontrast 2D TOF MRV shows nonvisualization of the left transverse sinus suspicious for dural venous sinus thrombosis
A repeat post contrast MRV was performed the same day that showed **no thrombosis** of the left transverse sinus.

Therefore, MRV with contrast is useful to confirm suspected dural venous sinus thrombosis seen on the noncontrast MRV.
B. Dural venous sinus thrombosis

10 yo boy with AML

Filling defect in the left sigmoid sinus
Sagittal 3DT1 axial images obtained after intravenous contrast administration shows a filling defect above the superior sagittal sinus

10 yo boy with AML

Granulocytic Sarcoma - Chloroma

Granulocytic Sacroma (Chloroma)
Granulocytic Sarcoma (Chloroma)

Same 10 yo boy with AML

The chloroma appeared to be contiguous with the left sigmoid sinus
Leukemic infiltration of the skull base and a chloroma over superior sagittal sinus both exhibit low ADC signal.

Low T2 signal is characteristic for granulocytic sarcoma.
C. PRES

PRES can be caused by induction of chemotherapy resulting in the characteristic vasogenic edema (bright signal on the ADC map) seen in the parietal and occipital lobes that subsequently resolves.

If left untreated, cytotoxic edema (low signal on the ADC Map) can result.

Vasquez et al Radiographics 2011;21:1123-1139
11 yo with ALL status post BMT (bone marrow transplant)
C. PRES

In this case, a 3 yo boy with acute lymphocytic leukemia was treated with intrathecal cytarabine, L asparginase, danorubicin and vincristine presented with disorientation. Ten days later symptoms resolved.

MRI demonstrates increased DWI signal in the subcortical white matter of the posterior parietal occipital lobes that resolved one week later.
Here, instead of increased diffusivity we see restricted diffusion surrounding central areas increased diffusivity on the ADC map that subsequently resolved compatible with PRES and complicating cytotoxic edema.
C. PRES

3 yo boy with ALL

FLAIR axial

FLAIR axial 10 days later
D. Infarction

3 yo girl with resected suprachiasmatic astrocytoma
E. Cavernous angiomas & microhemorrhages

17 yo boy underwent surgery chemotherapy and radiation surgery for medulloblastoma

T2 axial

SWI axial
3. Infection

Therapy including allogenic hematopoietic stem cell transplantation, steroid therapy, chemotherapy and radiation therapy as well as immunosuppression places the child at risk for developing CNS infections.

Life threatening infections are caused mainly by viruses or fungi.

“Fungal cerebral abscesses may have central restricted diffusion similar to that of bacterial abscesses, which is likely due to highly proteinaceous fluid and cellular infiltration. “

_Vasquez et al Radiographics 2011;21:1123-1139_
Fungal infection

For example, this 9 yo girl with 2 weeks of headaches and fever, easy bruising and leukocytosis was discovered to have AML and a fungal intracranial infection.
4. Therapeutic Complications

- I. Surgical
- II. Radiation
- III. Chemotherapy
- IV. Immunosuppression/bone marrow transplantation
I. Surgical Complications

- The quality of surgical resection is a major prognostic factor in pediatric CNS tumors

- Due to surgical technical advances, mortality is less than 1%
I. Surgical Complications

- Cerebrospinal fluid leak
- Cranial nerve palsy
- Hydrocephalus
- Hemorrhage
- Cerebral edema
- Infarction
- Wound infection
- Cerebellar mutism from resecting vermian tumors
I. Surgical Complications

3 yo boy status post surgical resection of a medulloblastoma

Pseudomeningocele
II. Radiation therapy can induce

- Cavernous angiomas
- Meningiomas
- Microhemorrhage
- Osteosarcoma

Less commonly:
- Glioblastoma
- Atherosclerosis
II. Radiation Therapy

For instance, this is a case of a 17 yo boy who underwent surgery, chemotherapy and radiation therapy for a medulloblastoma.
Same patient
• Why is this not a meningioma?
  • Extensive surrounding edema
  • Intraparenchymal not extra-axial

• FLAIR: excellent tool for evaluating GBM
  • Cortical thickening
  • Architectural distortion
  • Surrounding edema
III. Chemotherapy

• Methotrexate is a common cause of neurotoxicity. It is a folate antagonist

• Metabolic derangements result from methotrexate-induced folate deficiency and may be reversible if treated early

Guleria S et. al, Neuroimaging in Toxic Brain Injuries ASN 2011
III. Chemotherapy

- Risk factors for methotrexate-induced neurotoxicity include high-dose treatment, intrathecal treatment, young age and cranial radiation.

- Damage to the white matter is referred to as leukoencephalopathy (LEP). “The hallmark of LEP is hyperintensities on T2-weighted imaging. In methotrexate-induced neurotoxicity these T2 hyperintensities are typically located in the periventricular white matter, particularly in the centrum semiovale.”

Fisher MJ et al AJNR 26:1686-1689
III. Methotrexate LEP

3 yo with ALL status post methotrexate administration

T2 prolongation within the deep white matter is seen with increased diffusivity noted on diffusion imaging
III. Methotrexate LEP

9 yo girl with ALL status post intrathecal and intravenous methotrexate

7 months later
III. Chemotherapy

13 yo status post intrathecal chemotherapy

Developed spontaneous hypotension
IV. Bone Marrow Transplantation

- Immunosuppression from allogenic hematopoietic stem cell transplantation and steroid therapy predisposes the patient to developing CNS infections
Influenza B

15 year old boy with ALL and secondary AML status post BMT and orthotopic heart transplant had high protein in CSF and was later found to have influenza B
Influenza B

2 weeks later
5. Metastases or secondary neoplasm

“Metastases of somatic cancers to the brain are common in adults with cancer, with approximately 25-35% of adult patients developing intracranial parenchymal lesions. By contrast central nervous system metastases are much less common in most extracranial pediatric solid tumors.”

Nichole J. Ullrich, MD, PhD and Scott L. Pomeroy MD, PhD Cancer Neurology in Clinical Practice p 607
5. Metastases

This is the MR of an 11 yo boy with medulloblastoma.
5. Metastases

5 year old girl with right shoulder pain

Normal T2 axial

Rhabdomyosarcoma
5. Metastases

8 months later

Tumoral dissemination to the basilar cisterns and leptomeninges
5. Drop Metastases to the spine

*In the same patient*

\[ T1 + gad \]
5. Metastasis

- 4-1/2-year-old boy who was diagnosed with a renal rhabdoid tumor
5. Metastatic renal rhabdoid tumor

The left temporal thalamic lesions shows susceptibility artifact, likely due to blood products.
Apart from the hemorrhagic metastatic deposit to the left temporal thalamic region (blue arrow), he also developed metastasis to the pineal gland (yellow arrow). No susceptibility artifact was present in the pineal gland.
6. Endocrine Complications

- Endocrine complications are common in childhood cancer survivors, affecting between 20 – 50% of individuals who survive into adulthood. Most endocrine complications are the result of prior cancer treatments, especially whole brain radiotherapy.

  Chematitilly W et al Endocrine-Related Cancer 2010 17 R141-R159

- In addition suprasellar or sellar masses can cause panhypopituitarism.
6. Endocrine Deficiencies

GH deficiency - XRT
Precocious puberty - XRT
Hypogonadotrophic hypogonadism - XRT
ACTH deficiency - surgery or XRT
TSH deficiency – glucocorticoids or XRT

Chematitilly W et al Endocrine-Related Cancer 2010 17 R141-R159
6. **Endocrine complications**

8 mo F with short stature after treatment for a suprasellar hypothalamic tumor

She developed anterior hypopituitarism
6. Endocrine complications

A 9 year old girl presented with panhypopituitarism and was confirmed to have a germinoma after transphenoidal biopsy.

After radiation therapy to the craniospinal axis, the pituitary mass resolved and the pineal gland became smaller.
Conclusion

There are a wide range of potential complications and it can seem a bit daunting to consider them all. Therefore, I hope the checklist provided may serve as a useful tool to screen for some of the more common complications:

1. Mass effect
2. Vascular compromise
3. Infection
4. Post therapy effects
5. Metastasis or secondary neoplasms
6. Endocrine complications
Conclusion

The incidence of cancer in the United states is on average 1/10,000 children per year. With increasing survival time after treatment, CNS complications have become more common. Early detection and awareness of potential complications can help initiate early treatment and thereby improve outcome as well as quality of life.

Thank you!

Mia S. Kelly
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