Managing Neurologic Sequelae of Brain Tumors in Children

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Childhood Brain Tumors ~5 per 100,000 person-years





Symptoms of a Brain Structural Lesion

- Increased intracranial
 pressure
 - Headache
 - Increased head circumference
- Focal neurologic signs



Headache Symptoms Suggesting Increased ICP

- Headaches that are unresponsive to previously effective therapies
- Change in prior headache pattern
- Awakens child from sleep
- Vomiting
- Focal symptom or sign
 - Cranial Nerve VI palsy
- Papilledema



Focal Neurologic Signs/Symptoms

- Cerebellum
- Brainstem
- Optic pathway
- Hypothalamus
- Pituitary
- Cortex
- Pineal

Ataxia, nystagmus Gait change, cranial nerve palsy Visual acuity/fields Failure to thrive, hormonal changes, abnormal vision Hormonal insufficiencies Seizures, focal deficits Parinaud's syndrome

Neurological/Neurocognitive effects of treatment

- Surgery
- Chemotherapy
- Radiation therapy

Neurosurgery Late Effects

 Neurologic/sensory deficits after surgery are specific to location and in part reflect those caused by the tumor itself



- Neuropsychological deficits
 - Attention, memory, processing speed
- Endocrine dysfunction
- Psychological/adjustment issues

Cerebellar Mutism Syndrome

- Occurs postoperatively, 15–25% of patients with tumors in the cerebellar midline
- Delay of 12-48 hours post surgery



- Loss of verbal expression, irritability, ataxia, poor attention and eye contact, vomiting, incontinence, emotional lability
- Speech recovery in days to many months
 - Mild: recovery <1 week</p>
 - Moderate: recovery 1-4 weeks
 - Severe: recovery >4 weeks, often with long-term disability

Chemotherapy-related Neurologic Effects

- Increasing frequency as a result of aggressive therapy and prolonged survival
 - Direct toxic effects or indirect from metabolic encephalopathies or infections
 - Effects may be confused with disease progression
- Many novel, biologic agents now seen to have neurologic effects



Acute Drug-induced Encephalopathy

- Agents: Chemotherapy, immunosuppressive agents or steroids (often dose-dependent and drug-specific)
- Chemotherapy-induced encephalopathy rare with notable exceptions
 - Ifosphamide induces encephalopathy in 15% of patients, most commonly with confusion due to reversible mitochondrial inhibition
- Decadron can produce encephalopathy
 - Ranges from subtle manic mood to psychosis and delirium
 - Reduction or cessation of steroids may be necessary

Chemotherapy Late Effects

- Hearing Dysfunction
 - cisplatin, carboplatin; worse combined with radiation
- Peripheral Nerve Damage
- Cerebral white matter damage/leukoencephalopathy
 - methotrexate, ifosfamide
- Neurocognitive Effects
 - Intravenous and intrathecal treatments
 - High-dose intravenous methotrexate
 - High-dose chemotherapy with bone marrow transplant
- Secondary cancers/leukemia

Toxic Peripheral Neuropathy

- Typically motor, but can have sensory component
- Most common culprits: vincristine, thalidomide
- Neuroprotective therapies have not been successful in preventing toxicity
- Withdrawal of the agent may not halt progression
- Incidence largely dependent on cumulative dose

Radiation Therapy Cognitive Effects

- Age/dose are critical
- Detrimental effects more pronounced over time



Packer et al. J. Neurosurg. 1989

Merchant et al. J Clin Oncol. 2009

Post radiation strokes in survivors of brain tumors and leukemia



Bowers D et al. J Clin Oncol 2006

Radiation-induced vasculopathy

- Vasculopathy is dose dependent and may be linked to underlying genetic disorder
- Risk is sustained, lifelong



Ullrich et al. Neurology 2007

Endocrine dysfunction

- Hormonal deficits are related to focal injury from tumor/surgery and to radiation dose
- Pituitary hormone deficiencies
 - <u>Anterior pituitary</u>: GH, TSH, FSH/LH, prolactin, ACTH
 - <u>Posterior pituitary:</u> Vasopressin, Oxytocin
- Diabetes insipidus
- Precocious puberty
 - Hypothalamic astrocytoma /optic pathway glioma
 - Germinoma



Figure 5 Incidence of endocrinopathy after > 40 Gy irradiation of the hypothalamus.

Lawrence et al. Int J Radiat Oncol Biol Phys. 2010

Clinical Example: Craniopharyngioma

- The most common brain tumor of nonglial origin in children
- More than 50% occur in patients under age 21
- 3-6 % of most pediatric brain tumor series

Clinical Presentations

- Endocrine dysfunction: delayed growth or other manifestations of hypopituitarism
- Visual disturbance: can be very severe, progressive loss of vision my occur unnoticed by patient or family
- Increased intracranial pressure when tumor obstructs third ventricle and causes hydrocephalus: nocturnal or morning headache
- Personality change or confusion

Radiology of Craniopharyngioma



DEVELOPMENTAL ORIGIN







Neurosurgical Approach



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Treatment options and outcome

Total or subtotal resection of mass followed as needed by fractionated radiation therapy

British Columbia 1967 – 2003 (n=41)
All children diagnosed included in Provincial registry
Age at follow up 11.9 – 36.9 years
Ten year overall survival: 84%

Nine deaths:

epilepsy diabetes insipidis stroke

multiorgan failure/endocrinopathy

progressive disease in only one patient Visser, et al., J Neurooncol 2010; 100:105-111

One survivor at Boston Children's died of cardiac arrhythmia Mong et al., Ped Neurol 2008; 38:256-260



Outcome of Craniopharyngioma

- Death from recurrent, progressive tumor is uncommon
- Sequelae from this otherwise "benign" tumor can be severe and often life changing, sometimes life threatening
- Multiple organ systems are affected
- Multidisciplinary care needed for follow up

BITEMPORAL HEMIANPOSIA



Visual Disturbance

- Bitemporal hemianopsia is classic presentation – variable recovery, but if recovery occurs it generally occurs early
- Less commonly all vision is lost in one or both eyes
- Ophthalmology follow up is key, at times a low vision program is necessary

FUNCTIONS OF THE PITUITARY



Hormonal Insufficencies

- Diabetes Insipidus due to vasopressin (antidiuretic hormone or ADH) insufficiency
- Replacement with oral or intranasal DDAVP
- Thyroid, adrenal and growth hormone insufficiency common; sex hormone (LH/FSH) or prolactin insufficiency less
- Endocrinology follow up is essential

CRANIOPHARYNGIOMAS:

IMPACT ON THE SUPRASELLAR REGION



HYPOTHALAMIC OBESITY



Sleep Disturbance and Daytime Somnolence

- Daytime somnolence is common
- Careful history will often reveal nocturnal awakenings not related to need for urination or other stimuli
- Obstructive sleep apnea common especially in association with obesity
- Disruption of circadian rhythms

CRANIOPHARYNGIOMAS:

IMPACT ON THE SUPRASELLAR REGION





LOSS OF CIRCADIAN CYCLING



Lipton et al., Neurology 2009

Melatonin Insufficiency

- Melatonin replacement can be helpful
- Stimulants may be needed to enhance daytime alertness
- Some benefit from very bright lights in morning
- Daytime somnolence may be quite troublesome: should also check for GH insufficiency

Memory and Organization Deficiencies

- Despite normal IQ, craniopharyngioma survivors often struggle in school
- Disabilities from vision deficits, obesity, multiple hormonal insufficiencies and altered circadian cycles may contribute
- Focal deficits in cognitive function not well represented on standard neuropsych testing are a major contributing factor

LIMBIC SYSTEM



Memory and Organization Deficiencies

- Despite normal IQ, specific weaknesses in short term memory are common
- Difficulties with organization
- Slow processing of information
- An IEP or 504 plan often needed, and especially specific aids for memory and organizational deficits can be very helpful

Carpentieri et al. Neurosurgery 2001

Long Term Outcome of CNS tumors

- Childhood cancer survival study cohort
 - Diagnosis 1970-1986; N=2888; 25% no radiation
 - Neurocognitive questionnaire N=802
- 82% one chronic condition; 38% serious
 - Medical complications associated with increased impairment
- Neurocognitive impairment rate high
 - Significantly greater than non-brain tumor survivors or siblings
- Radiation associated with worse cognitive outcome as well as low employment/marriage/emotional problems
 - 36 Gy CNS > 24 Gy ALL > ALL (no Radiation)

Disease and Host Factors

- Disease/treatment related
 - Chemotherapy
 - CNS involvement with ALL
 - CNS tumor size/location
 - Cranial nerve deficits
 - Radiation dose/field
 - Endocrine dyscrasia
 - Fatigue
 - Hearing loss
 - Hydrocephalus
 - Neuropathy
 - Posterior fossa syndrome
 - Relapse
 - Steroid use
 - Stroke/vascular disease
 - Time from treatment

- Host/environment related
 - Age at diagnosis/evaluation
 - Baseline IQ
 - Educational supports
 - Genetic background
 - Gender
 - Socioeconomic status
- Neurocognitive/social
 - Deficits in attention, memory, processing speed, executive function
 - Expectations
 - Friends/social interactions
 - School absences
 - Missed peer experiences
 - Emotional distress
 - Self image/confidence

Summary

Cancer Survivors Need Multidisciplinary Support

- Medical and Neurological Needs
- Neuropsychological assessment
- Educational/vocational
 - IEP/504 plans
 - Technical support
 - Hearing aids, books on tape, computers, assistive devices
- School consultation programs
- Psychological and psychosocial support is critical
 - Risk of social isolation