NEURO-OPTOMETRY ONCOLOGY

Primary Brain Tumors and their Clinical Manifestations

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NEURO OPTOMETRY

- 20% of all patients seeking medical treatment have neurological problems, either as the presenting complaint or as an associated condition complicating the primary illness.
- Neuroscience principles and nervous system disease must be well understood due to its close relationship to the visual system and visual pathways.
- Eye-care facilities are frequently the first place patients go with symptoms of central nervous system disease.

Who Gets Brain Tumors and Why

- Genes: Genetic predisposition is less than 5%, most involve chromosome 17 (P-53 gene)
- Illness: Neg. history of H.Z. or chicken pox and neg. history of allergies and colds leads to an increase in the risk of glioma??? Immune system???
- Trauma: Head injury ↑ risk of meningioma
- Pesticides: ↑incidence in tumors in children exposed before birth (Flea/tick especially)
- Petro chemical: ↑ risk… etiology???

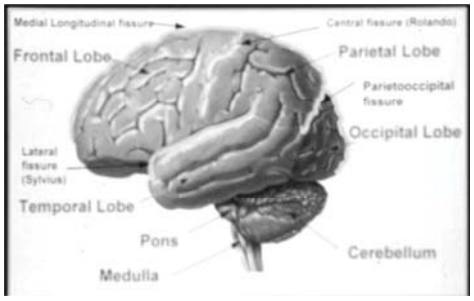
Who Gets Brain Tumors and Why

- Approximately 29,000 new cases or primary brain tumors diagnosed per year. 13,000 will die.
- Incidence:
  - 11/100,000 overall,
  - 6/100,000 malignant,
  - Average age 55 years old,
  - Greatest incidence is >65 years old.
- Ethnic: Japan: less ½ of incidences of northern Europe
- Gliomas: Whites > Blacks - Meningiomas: Blacks > White
- Gliomas: Men > Women - Meningiomas: Women > Men

WM * Glioma BF * Meningioma

Frontal Lobe

ANATOMICAL STRUCTURES OF THE BRAIN



Frontal Lobe

- Contains most of the dopamine-sensitive neurons in the cerebral cortex. The dopamine system is associated with reward, attention, long-term memory, planning, and drive.
- Emotional control center, home to our personality, controls our social behavior and inhibits the limbic system thereby controlling impulsive behavior.
- Motor function originates in the frontal lobe, as does problem solving, memory, language, and judgment.
- Frontal lobe also contains Broca's area which gives us our ability to verbalize.

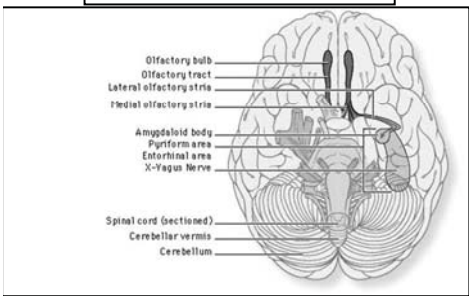
Frontal

- 30% of all tumors occur in the frontal lobe
- There is an increase in seizures and 50% result in papillaedema
- Lesions in the frontal lobe frequently result in apathy, depression, and abulia (lack of spontaneity), lethargy, feelings of indifference
- Lesions can produce exaggerated personality traits

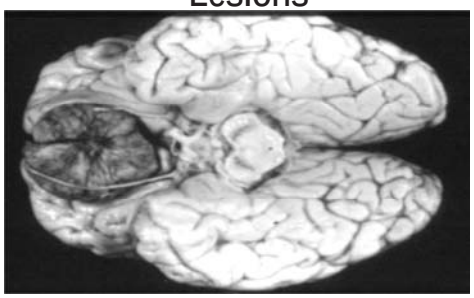
Foster Kennedy Syndrome Frontal Lobe

- Foster Kennedy Syndrome: ipselateral optic atrophy and contralateral papillaedema (meningiomas, tumor of olfactory system, gliomas)

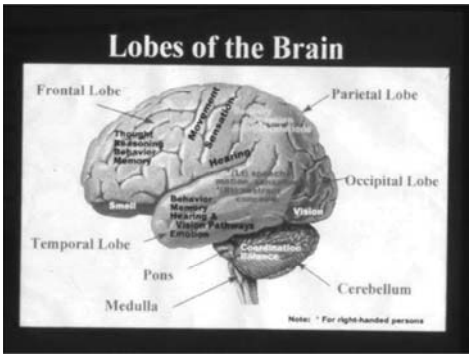
OLFACTORY AREAS



Neoplasms and Related Lesions



Temporal Lobe



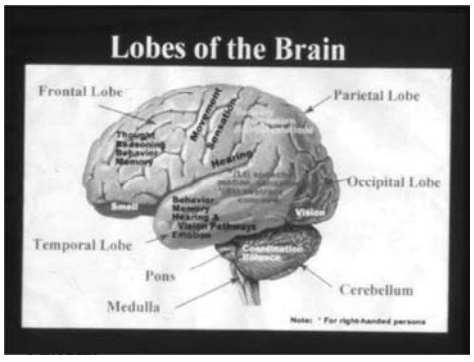
Temporal Lobe

- Primary auditory perception
- Contains Wernicke's area which spans the region between temporal and parietal lobe; which in tandem with Broca's area is responsible for our ability to understand and respond to spoken words.
- Center for abstract thought
- Temporal lobe contains the hippocampus and plays a key role in the formation of long- and short-term memory
- 20% of all tumors

Temporal Lobe Lesions

- Similar to Frontal (personality changes)
- Greatest frequency in convulsions (Jacksonian)
- Visual hallucinations
- Dominant: Wernicke's Asphasia, ↓ write or understand meaning of spoken words, ↓ comprehension, meaningless speech
- Non-Dominant: ↓ mental function, ability to judge special relationship
- Impaired long-term memory
- Altered personality and affective behavior
- Altered sexual behavior

Parietal Lobe



Parietal Lobe

- Major area for sensory stimuli interpretation and interpretation of visual symbols
- Integrates sensory input, primarily with the visual system
- Constructs a spatial coordinate system to represent the world around us
- Center for navigation
- Major afferent/efferent communication with thalamus, cerebellum, and brain stem

Damage to the Parietal Lobe
(Left Dominant Side)

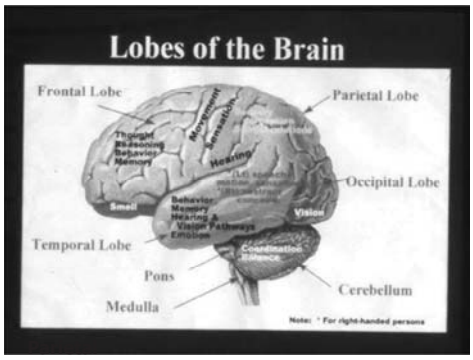
- **Gerstmann's Syndrome**
  1. Difficulty with writing (agraphia)
  2. Difficulty with mathematics (acalcula)
  3. Disorders of language (aphasia)

- Sensory agnosia: abnormalities in sensory perception despite normal sensory pathways
  - Close eyes…object in hand, confusion as to identity

Damage to the Parietal Lobe
(Right non-Dominant Side)

- Neglecting parts of body or space (contralateral neglect)
- Impairs many self-care skills such as washing and dressing
- Denial of deficits (Agnosia) . Visual field defects go unnoticed vs. temporal lobe defects, which are noticed
- Decrease in drawing abilities; also, loss of orientation…navigation (point A to point B)

Occipital Lobe



Occipital Lobe

- Auras
- Decrease Visual Acuity
- Visual Field Defects

Occipital Lobe

✓Migraine: begin centrally - expand peripherally, usually headache involves side opposite field loss.

✓Anton's Syndrome:

Denial of Cortical Blindness

Complete loss of vision often without awareness.

Normal pupillary reaction

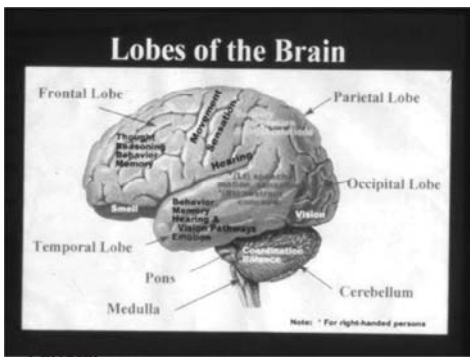
Normal opthalmoscopy

Loss of reflex closure

Occipital Lobe

- Charles Bonnet Syndrome
  - Well-formed visual hallucinations due to sensory deprivation
  - Common in elderly patients with vision loss, 11% of low-vision patients
  - Early marker for dementia

Cerebellum



Cerebellum

- Posture, muscle tone, coordination
- Plays an important role in motor control
- Involved in cognitive functions such as attention and language
- Does not initiate movement, but does contribute to coordination, precision, and accurate timing
- Because of fine-tuning function, damage to the cerebellum does not cause paralysis; but instead produces disorders in fine movement, equilibrium, posture, and motor learning.
- Ipselateral structure

Tumors

Tissues of the Central Nervous System

- Gliomas:
  - All primary tumors of the brain and spinal cord are composed of glial cells; this is where tumors develop.
  - Adult nerve cells cannot divide – hence they cannot form tumors

Tissues of the Central Nervous System

- Neuroglia Cells or Supportive Cells
  - Astrocytes Cells
  - Oligodendroglia Cells
  - Ependymal Cells
  - Schwann Cells

Tumors: Destruction

- Invasion: pressure from growing mass blocks blood vessels; causes local tissue death, which results in a decrease in mechanical resistance and furthers the spread
- Tumor cells: high levels of hydrolases (protease and collagenases) cause lytic damage to adjacent normal tissue
- Deprive surrounding cells of vital nutrients necessary for survival

Astrocytes

- Functions include:
  - biochemical support of endothelial cells which form the blood-brain barrier
  - the provision of nutrients to nervous tissue
  - maintenance of extra-cellular ion balance
  - a principal role in the repair and scarring process of the brain and spinal cord following traumatic injuries
- Pathology
  - Tumors
  - Tuberous sclerosis: Tumor-like nodules of the brain

TUMORS OF ASTROCYTE CELLS

Astrocytoma: Three types

Low grade- Pilocystic and Subependymal

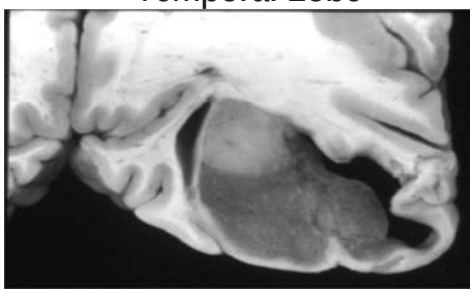
Mid grade- Anaplastic Astrocytoma

High grade- Glioblastoma Multiforme and Glioblastoma Cerebri

Low Grade Astrocytoma Grade I & II

- Typically non-infiltrating, but can invade surrounding tissue
- Metastasis is Rare
- Occur Mainly in Children
- Location: Cerebellum & Optic Tract

Astrocytoma of the Temporal Lobe



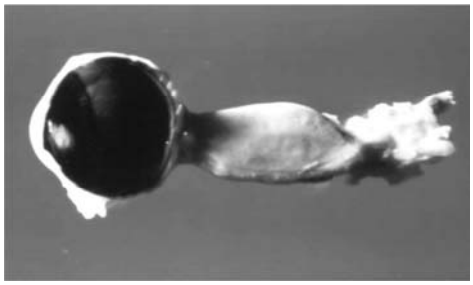
OPTIC NERVE AND CHIASMAL ASTROCYTOMA

- Gliomas of visual system: 5% of orbital tumors
- 70% of patients are under age 10
- Substantial visual loss
- Involve chiasm > optic nerves

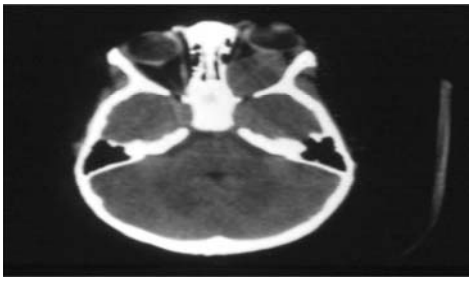
OPTIC NERVE AND CHIASMAL ASTROCYTOMA

- Optic Nerve Gliomas
  - Most are low grade astrocytoma
  - 20% have recurrences
  - 15% die
  - 85% survive 20 years
- Chiasmal Gliomas (Less Favorable)
  - 33% have recurrences
  - 50% survive 20 years
  - Death due to local extension

Astrocytoma of the Optic Nerve



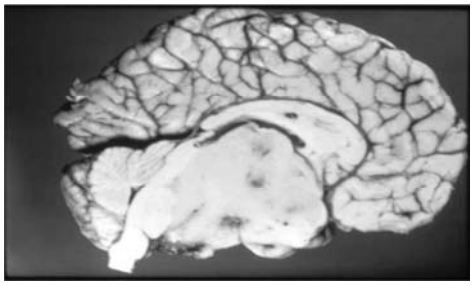
Astrocytoma of the Optic Nerve



Mid-Grade Astrocytoma

- **Grade III**
  - Grow More Rapidly
  - Recur More Frequently
  - 65%-70% Survive 1 Year
  - 40% Survive 2 Years
  - 15% Survive 5 Years or More

Astrocytoma of the Optic Chiasma



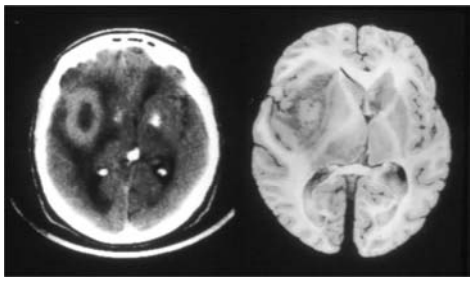
High Grade Astrocytoma Grade IV

- GBM 30% of All Primary Tumors
- Can Double in Size Every 10-11 Days
- Seizures Occur in 30%-40% of Cases
- Symptoms: Headache, Personality Changes, Papillaedema, Vomiting
- Fewer Than 20% Survive 12 Months

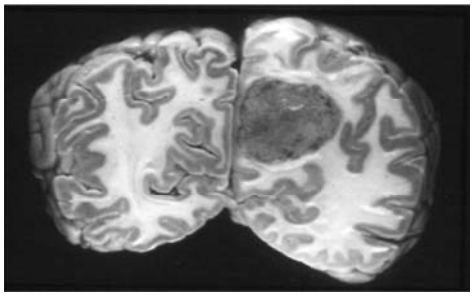
Glioblastoma Multiforme

- Fairly constant occurance worldwide
- Little change in morbidity in past two decades
- Age 40-60; W>B; M>W 3:2
- Etiology is unknown, however:
  - Adult lesions appear to have defect on chromosome ten
  - Children have a transformation of a lower grade tumor
- PET scan (Positron Emission Tomography)
- Average survival over age 40 is 6 months, under 40 is 18 months

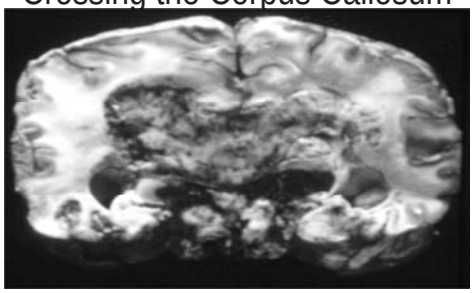
Glioblastomas



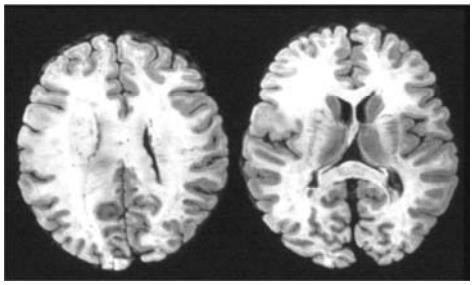
Glioblastomas



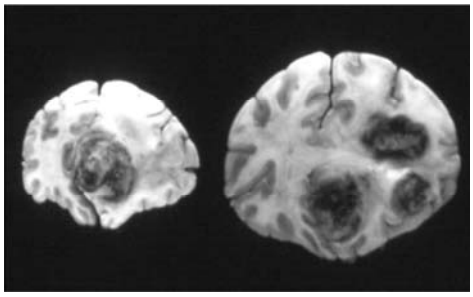
Glioblastomas Crossing the Corpus Callosum



Disseminating Glioblastoma



Glioblastoma



Chemotherapy For Glioblastomas

- Gliadel Wafer
  - Used to deliver carmustine (nitrosourea oncolytic agent)
  - Alkylation of DNA and RNA
  - Used in treatment of Glioblastoma Multiforme

Gliadel Wafer cont.

- **Kills Tumor Cells Immediately**
- **Kills Tumor Cells on Replication**
- **Cytotoxic**
  - **Nitrosoureas (BCNU, CCNU)**
    - **Most Frequent**
    - **No Hair Loss CTX**
- **G.I., Mucosal Tissue, Irritation**

- GLIADEL WAFER

Gliadel Wafer (Carmustine) t/x: average is 18 months survival; vs placebo at 16 months

New t/x For Glioblastoma Multiforme

- Cleveland Clinic utilizes MRI-guided laser
- Thin probe inserted through small hole in skull which delivers heat to tumors without harming healthy tissue

NEW TREATMENT

- Preston Robert Tisch Brain Tumor Center
- Clinical trials for recurrent Glioblastoma

PVS-RIPO a genetically engineered Poliovirus

- A recombinant, live attenuated nonpathogenic oncolytic virus. The internal Ribosomal entry site (IRES) is replaced with (IRES) from Human Rhinovirus type 2, with potential antineoplastic activity.

PVS-RIPO

- Naturally infects almost all cancer cells because the receptor for the Poliovirus is abnormally present in most tumor cells.
- Due to Heterologous HRV2, only propagates in susceptible non neuronal cells (astrocyte cells GBM)

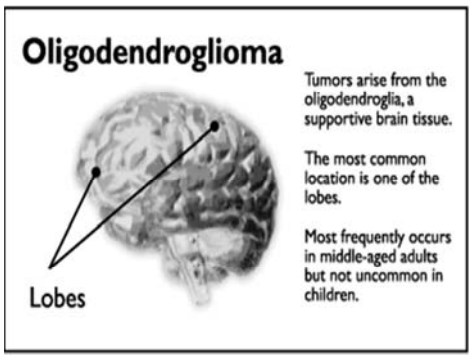
Continued:

- They are infused directly into the tumor, killing cells and causing immune system to attract tumor cells
- Future trials in other cancers such as pancreatic, prostate, lung and colon

Oligodendroglioma

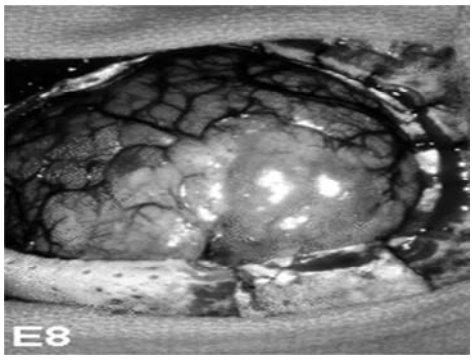
Oligodendrocyte

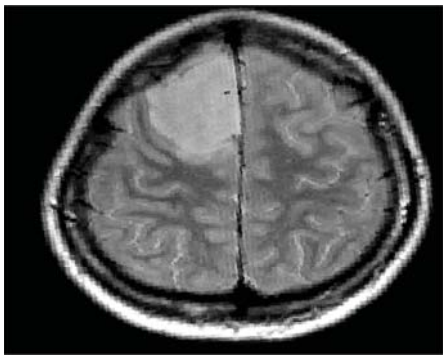
- Main function: insulation of axons (the long projection of nerve cells) in the central nervous system of higher vertebrates
- Pathology:
  - Tumors
  - Diseases that result in injury to the oligodendroglial cells include:
    - ★ Demyelinating diseases such as multiple sclerosis
    - ★ Cerebral Palsy: (damage to developing oligodendrocytes in the brain areas around the cerebral ventricles)

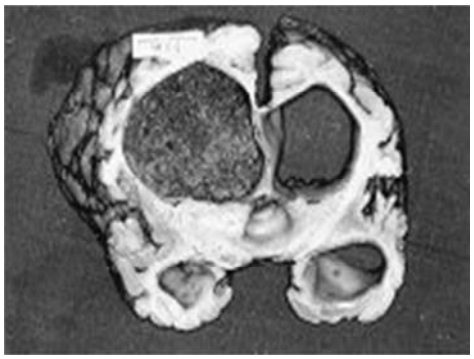


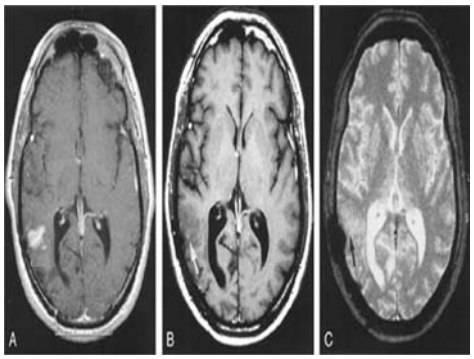
Oligodendroglioma

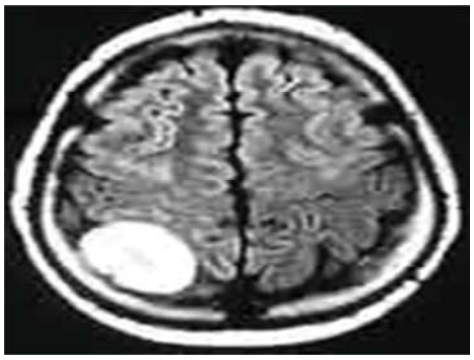
- 5%-7% of Gliomas
- 40%: 50yrs or above
- Males > Females
- Location: 40%-70% Frontal Lobe
- History of Chronic Seizure Disorder
- Usually mixed with malignant astrocytes
- Mean survival rate is 5 years



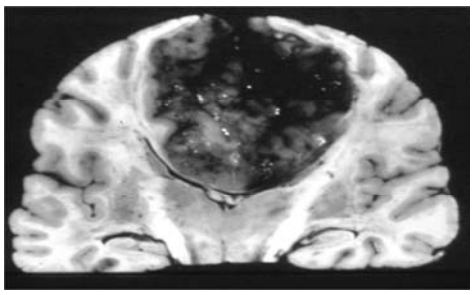




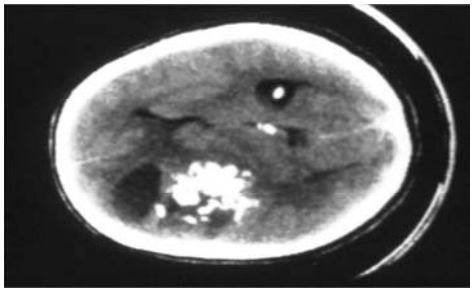




Oligodendroglioma



Oligodendroglioma



Mixed Glioma

- Contain both astrocytes and oligodendrocytes

- Behavior is similar to tumors composed of highest grade cell found in tumor

Cerebellar Tumors

- **More frequent in children - 40% gliomas**
- **Disturbances (Result in deficits)**
  - **Posture**
  - **Muscle Tone**
  - **Coordination**
- **Papillaedema - Almost constant sign**
- **Lesions in vermis:**
  - **Affects large movements of entire body & posture**
- **Lesions in hemispheres:**
  - **Ipselateral structure**
  - **Affects fine movements of extremities - arms, hands, legs, feet**

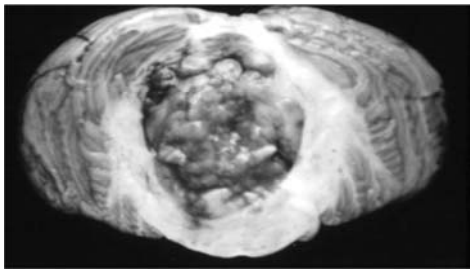
Cerebellar Tumors: Medulloblastoma

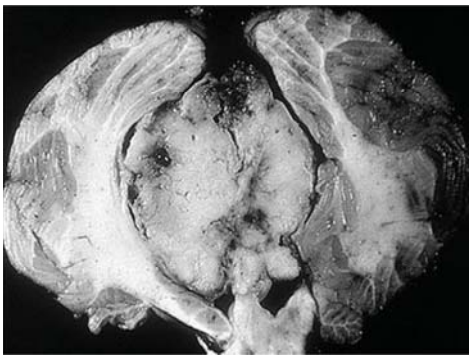
- Common childhood tumor
- 3 to 8 years old, peak at 8 years
- Boys 2x > girls
- Vomiting just after waking in a.m.
- Arise from vermis in children; lobes in adults
- Irritability, sluggishness, personality changes, trunkal gait
- Loss of suppressor gene on chromosome 17
- Severe headache
- Very responsive to radiation

Medulloblastoma cont.

- Can invade fourth ventricle, subarachnoid space, and cerebrospinal fluid pathways
- Comprise 18% of brain tumors in children
- Fast-growing
- 18% arise from embryonic cerebellum

Medulloblastoma





Primitive Neuroectodermal Tumor

- Identical to medulloblastoma but occurs in cerebrum
- Tend to grow large
- Increased intracranial pressure is common

Ependyma

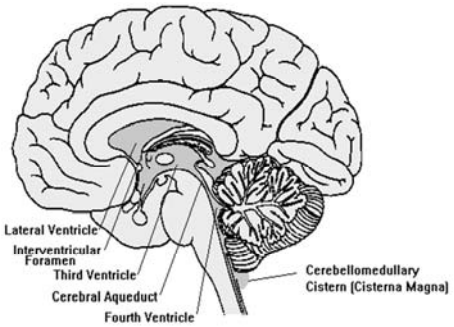
- Thin epithelial membrane lining the ventricular system of the brain and the spinal cord
- One of the four types of neuroglia in the central nervous system (CNS)
- Involved in the production of cerebrospinal fluid (CSF)
- Within the brain's ventricles, a population of modified ependymal cells and capillaries together form a system called the choroid plexus, which produces CSF

TUMORS OF EPENDYMAL CELLS Ependymomas

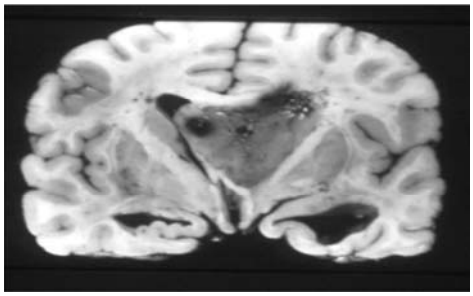
- Arise from lining tissue of lateral ventricle (6%)
- 5% of intracranial gliomas
- 10%-12% in children
- 60% under age of 5
- Location: 70% occur in fourth ventricle
- 60% have increased intracranial pressure
- Generally not responsive to radiation

Ependymomas

- Rapid seed along CSF
- 30% seizures, 60% papillaedema
- Nausea, vomiting, vertigo
- Watch for Abducens nerve paralysis in children
- Peak: under 15 years of age; a second peak between ages 20-25.
- Freq. Fourth…Lateral…Third…Aqueduct
- Infratentorial ependymomas:
  - 13% of infratentorial childhood brain tumors are enpendymomas which arise from the fourth ventricle



Ependymoma



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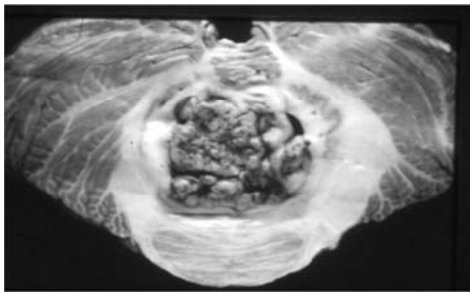

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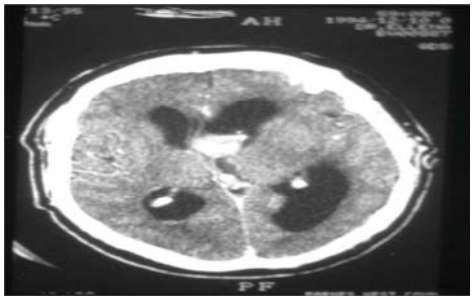

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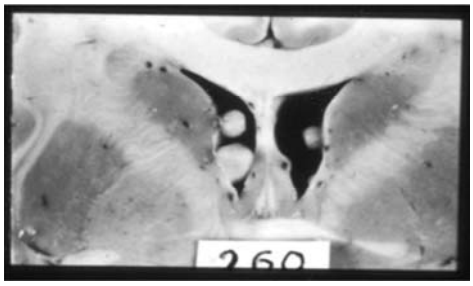


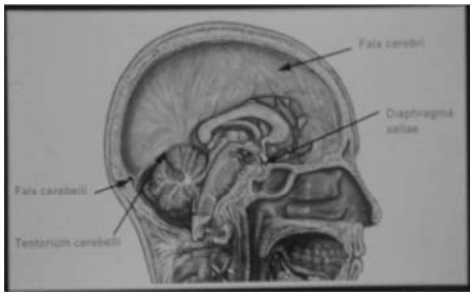
Childhood Tumors vs. Adult Tumors of the Central Nervous System

➢20% of childhood cancers are brain tumors

➢1-2% of adult cancers are brain tumors

➢Difference in Treatment

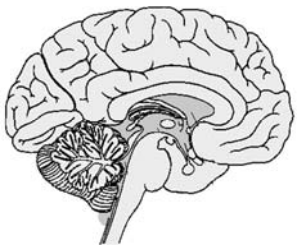
Meninges of the Brain



Difference in Adult and Childhood Brain Tumors

Adults: Supratentorial

Children: Infratentorial



Supratentorial Tumors

- Most adult brain tumors are supratentorial gliomas:
  - ◆Astrocytomas
  - ◆Oligodendrogliomas

Infratentorial Tumors

- Most childhood tumors are infratentorial:
  - ◆Cerebellar Astrocytomas
  - ◆Medulloblastomas
- 10% of childhood brain tumors arise from the pons or medulla
- Slow-growing
- May involve cranial nerves V-X (10%)

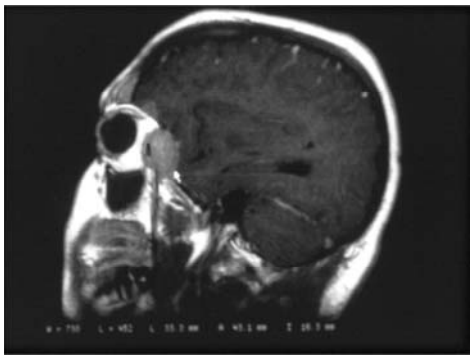
Non-Glial Tumors: Congenital Tumors of Neurons of the Nervous System

- Neuroblastoma
  - Neuroendocrine tumor of the sympathetic system
  - Most common cancer in infancy
- Retinoblastoma
  - Rapidly developing cancer which involves the cells of the retina
  - One of the best cure rates of all childhood cancers (95-98%)

Radiological Differences between Gliomas and Metastatic Carcinomas

DISTINCT DIAGNOSTIC MRI CHARACTERISTICS: METASTATIC vs. PRIMARY TUMORS

- 80% occur in cerebrum, 16% in cerebellum, 4% in brain stem
- **Lesions:**
  - **solid/spherical in shape**
  - **Well-defined margins**
  - **center is soft and filled with dead cells**
  - **zone of active tumor is ring-like**
- Growth in the junction between white/gray matter (rich in blood)
- 50% are multiple tumors : Lung cancer (non-small cell, oat cell), breast CA, or melanoma
- Renal/colon: frequently single tumors
- Frequent widespread edema



Determining the Degree and Extent of Malignancy

DEGREE OF DIFFERENTIATION

Grade I	**Well Differentiated:** Tumor closely resembles tissue of origin
Grade II	**Moderately Differentiated:** Less resembles tissue of origin, increase in variation inside cells
Grade III	**Poorly Differentiated:** Does not resemble tissue of origin, increase in mitosis
Grade IV	**Very Poorly Differentiated:** No resemblance to tissue of origin; worst prog.

Determining the Degree and Extent of Malignancy

STAGING OF TUMORS

Stage I	**Limited:** One anatomical region or organ
Stage II	**2 – 3 Regions:** Does not cross midline
Stage III	**Both Sides of Body:** May involve lymph nodes or spleen
Stage IV	**Multi-organ:** Bone marrow, lung, liver, spleen (worst)

Schwann Cells

- Schwann cells may be intracranial or peripheral, and may involve any nerve (sensory more common than motor)
- Function is to support neurons in the PNS
- Myelinating Schwann cells wrap around axons of motor and sensory neurons to form the myelin sheath, which aids in the conduction of nerve impulses

Tumors of Schwann Cells

Two Types of Schwann Cell Tumors

Both types arise from sheath of Schwann cells surrounding nerves

- Neurilemmoma
  - Neurilemmomas displace, rather than incorporate, neural structure. This action often permits salvage of affected nerve.
- Neurofibroma
  - Neurofibromas occur intraneurally, therefore tumor removal requires sacrifice of the involved nerve.

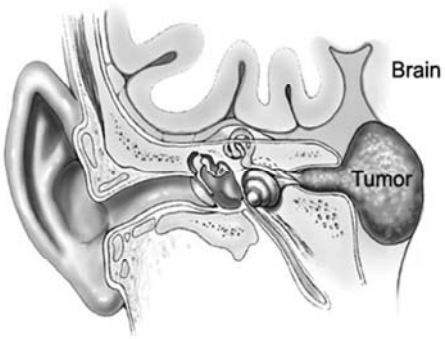
Neurilemmoma: Acoustic Neuroma

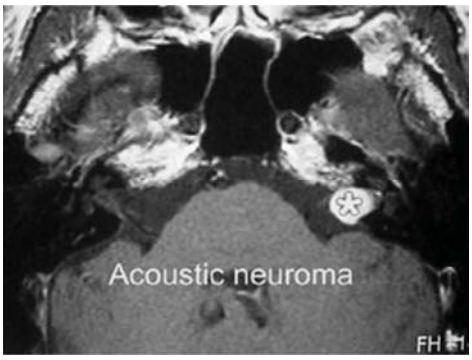
- Common over age 50
- Males = Females
- Location:
  - ◆Vestibular Division of CN VIII
  - ◆Acoustic Division of CN VIII
  - ◆V and IX can also be affected

Acoustic Neuroma:

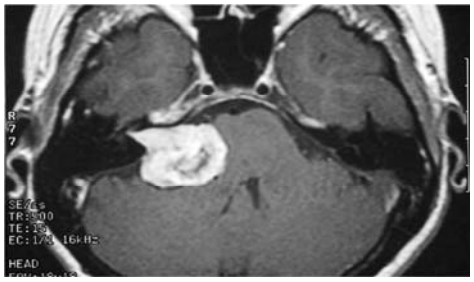
(Vestibular Schwannoma, Acoustic Neurilemmoma)

- CN VIII composed of vestibular portion (Balance) with Cochlear (Hearing).
- Slow-growing benign tumor of nerve-insulating Schwann cells. Tumor develops in internal auditory canal, can mushroom and press on brain stem
- As the tumor increases in mass, hearing loss, loss of balance, tinnitus, and facial numbness (V) occur.
- CN VII also occupies canal and can be stretched into ribbon-like fashion (Bells palsy)





Acoustic Neuroma



SYSTEMIC NEUROLOGICAL DISORDERS ASSOCIATED WITH NEUROFIBROMAS

Von Recklinghausen Neurofibromatosis

- Two types (Type I, Type II)
- Arise from Schwann cells
- 10% develop malignant neoplasms
- Increase in meningiomas
- Increase in a A/V malformations
- Spina bifida
- Increase risk of optic nerve astrocytomas
- Increase risk of retinal astrocytomas
- Increase risk of sarcomas
- Tumor is intra neural which means removal requires sacrifice of the nerve.

Von Recklinghausen Neurofibromatosis

•Type I.

•Autosomal dominant

•Café-au-lait spots: Increase in basal layer pigment

•Lisch nodules (iris hamartomas): spindle-shaped, melanin-producing cells in the iris

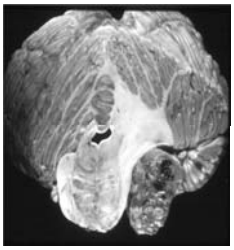
•Cutaneous neurofibromas

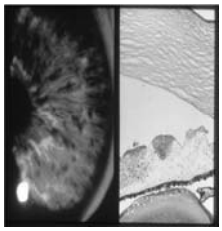
•Suspected defect on chromosome 17

Von Recklinghausen Neurofibromatosis, cont.

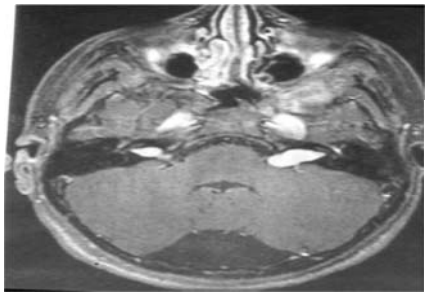
- Type II.
  - ◆Bilateral acoustic neuromas
  - ◆Few café-au-lait spots
  - ◆Suspected defect on chromosome 22

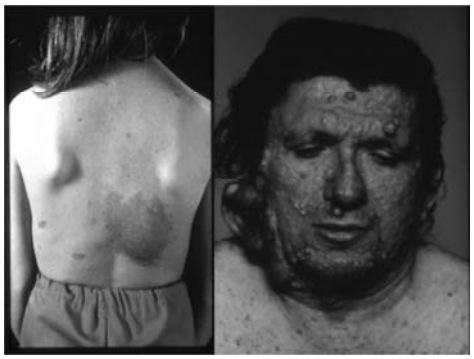
NEUROFIBROMATOSIS

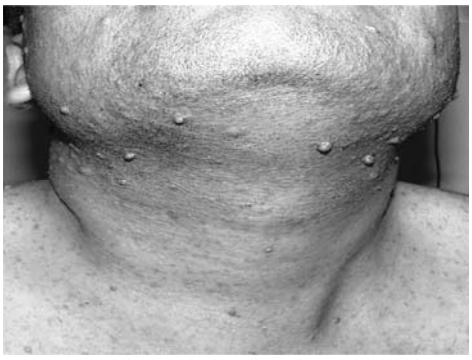


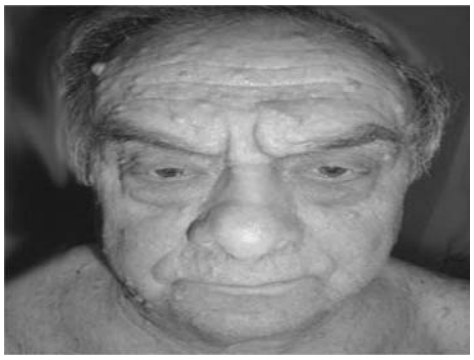


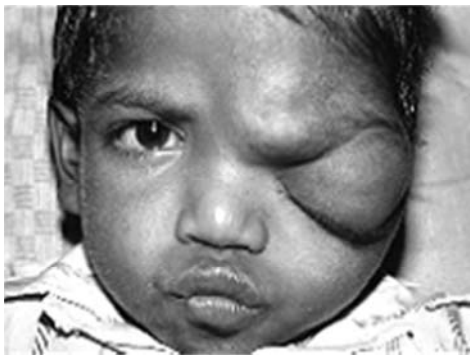
Bil. Acoustic











Benign Intracranial Tumors

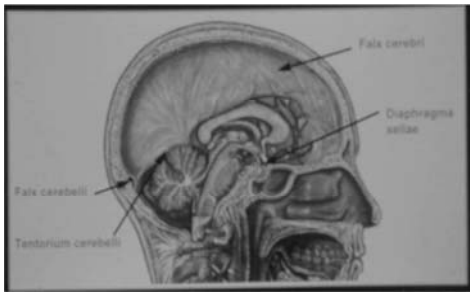
Meningiomas

The Meninges of the Central Nervous System

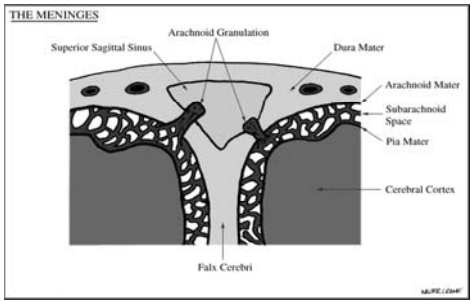
Meninges

- Structure:
  - -Dura
  - -Subdural
  - -Arachnoid
  - -Subarachnoid
  - -Pia
- The four meninge processes:
  - -Faux Cerebri
  - -Tentorium Cerebri
  - -Faux Cerebelli
  - -Diaphragma Selli

THE FOUR MENINGE PROCESSES



Layers of the Meninge Processes



Meningiomas

- 15% of All Intracranial Tumors
- 40-60 Years of Age
- Females 2x > Males
- 3%- 20% are anaplastic
- Location:
- Seizures and headaches are common
- Increased incidence in women with breast cancer

25%-Parasaginal Sinus
20%- Surface of the Brain
20%- Sphenoid Wing
10%- Olfactory Groove
10%- Supra Sella Region
10%- Posterior Fossa

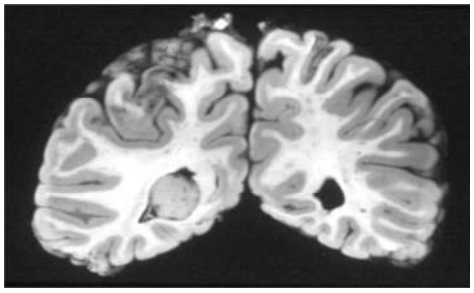
MENINGIOMA

- Originate: Dura mater or arachnoid membrane.
- Etiology: Uncertain, 70% have abnormal chromosome 22.
- Recurrence: 20% recur after 5 years, 30% recur after 10 years, 50% after 20 years
- 9% recur when considered 'complete removal'.

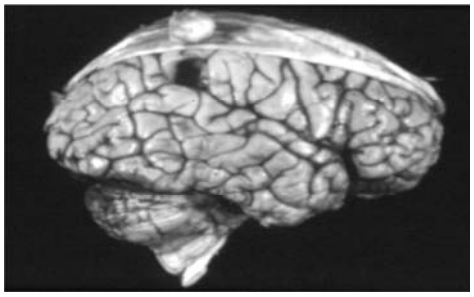
Meningiomas

- 70-80% have progesterone site, 9% have estrogen site
- Increase growth and freq. with pregnancy
- Increase in frequency and malignancy with radiation of any type

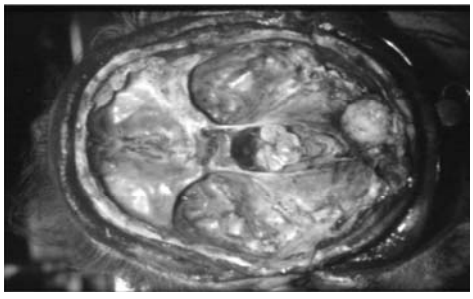
Meningioma



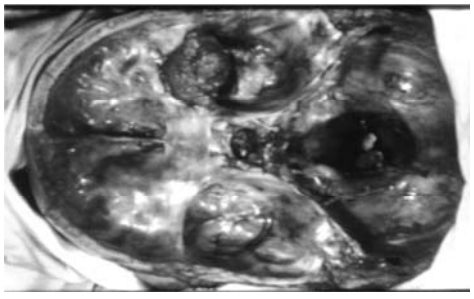
Meningioma



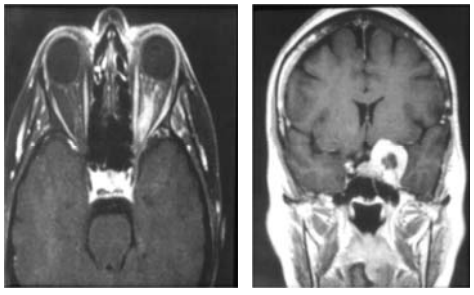
Meningioma



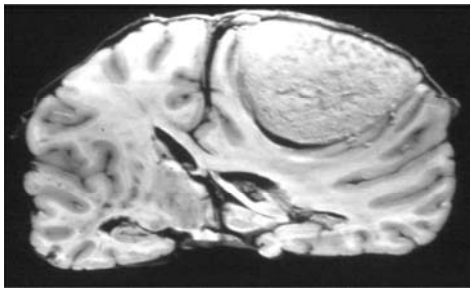
Meningioma



Meningioma



Meningioma



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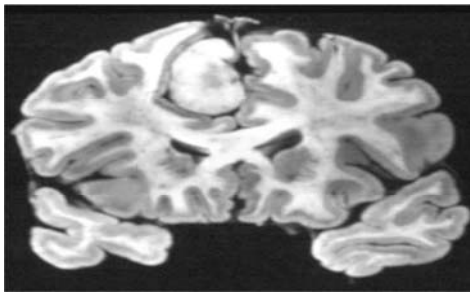
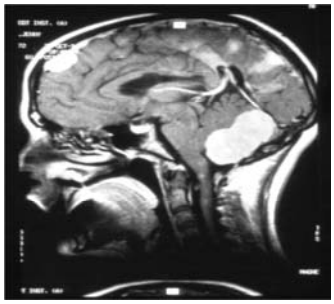


Meningioma

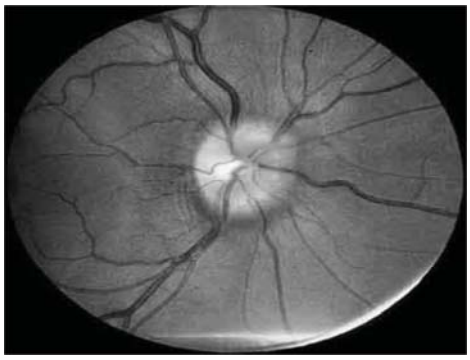


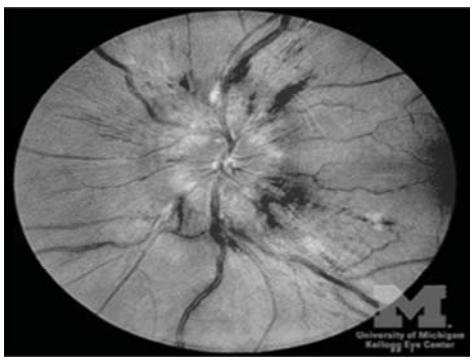
PAPILLAEDEMA:
TUMOR vs. PSEUDO-TUMOR CEREBRI

- Swollen optic nerve head frequent manifestation of primary tumors
- Must be differentiated from pseudo-tumor cerebri

Papillaedema

-↑CSF pressure 200 mm of water (100-180 norm) or 4.4-7.3 mmHg
-↑ Blind spot due to laterally displaced detachment of retina around optic disk
- Headache
- Nausea
- Bradycardia
- ↓ Swallowing
- Bilateral VI palsy due to compression of basilar artery
- Common third ventricle neoplasm





Pseudo-Tumor Cerebri

-↑CSF but with no localizing neurological finding
- Headache
- Nausea, vomiting
- Tinnitus (60%)
- VI Palsy (30%)
- Only morbidity is sensory vision loss
- 90% are obese, 90% women, 30 years of age average

Pseudo- Tumor Cerebri

➢Causes:
  ➢Previous inflammation to subarachnoid space giCSF flow
  - Hypercoagulate states
  - Endocrine Disorders (Cushing's Syndrome)
  - Nutritional (hyper Vit.A)
  - Anabolic Steriod
  - B.C.P., Tetracycline
➢Treatment:
  ➢Weight loss, Diuretic, Shunts, C.A.I.

Indications for Diagnostic Testing

Computed Tomography (CAT SCAN)

Indications for Use

- Craniopharyngioma
- Acute Stroke
- Subarachnoid Hemorrhage
- Intraorbital Foreign Body
- Better to Distinguish Some Neoplasm from Edema
- Acute Cranio-Cerebral Trauma

Radiological Diagnostic Testing

Plain Film

- Quick
- Less Costly
- Rule Out or Confirm Penetrating Foreign Body
- Rule Out Orbital Fracture But "Standard of Care" is CT

Computed Tomography

- Came in use in 1980's
- High levels of radiation (500x the amount of conventional chest x-ray)
- Amount of radiation received can vary greatly between patients
- Radiation-induced cancer takes roughly 20 years
- Risk factor for children is 10x greater than that of adults
- New units are reducing radiation levels

Computed Tomography

Iodinated Contrast Medium Enhances Visibility of Lesions

Contrast	**Non-Contrast**
Brain: Brain tumors, abscess, dementia, headaches	**Brain: any suspected hydrocephalus, poor renal function**
Sella: coronal plane	**Orbit: axial plane (due to high level of inherit orbital fat)**

M.R.I.

- Nikola Tesla (Croatian 1856-1943).
- Calibrated in Tesla units.
- Distinguishes between Hydrogen atoms in different environments.
- "Polarization" of Hydrogen atoms by MRI is different in normal and pathological tissue.
- Most MRI = 1 ½ T
- New MRI = 3T (2x as strong, 2x as fast)
- T1: chemical interaction, fat and bone are bright..M.S. reveals active lesions
- T2: molecules mobility, water and fluids are bright.(vitreous).. M.S. reveals long-standing lesions.

Magnetic Resonance Testing (MRI)

- Careful with patients with kidney disease
- Kidney disease or over 60 get a creatinine level and B.U.N.
  - Creatinine clearance rate (CrCl): the volume of blood plasma that is cleared of creatinine per unit time
  - B.U.N. (Blood urea nitrogen) test: measure of the amount of nitrogen in the blood in the form of urea, and a measurement of renal function
- Nephrogenic Systemic Fibrosis (NSF)
  - Rare syndrome that involves fibrosis of skin, joints, and eyes
  - Etiology is not fully understood
  - Seems associated with gadolinium In patients with severe kidney disease (trigger factor)
  - Patients develop hardened skin with fibrotic plaques and nodules
  - Resembles scleromyxedema

MRI Diagnostic Testing

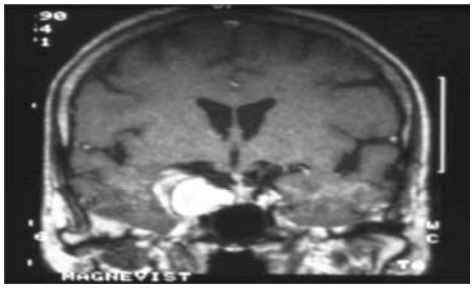
Magnetic Reasonance Imaging (MRI)
Gadolinium Enhancement (Magnavist) Increases Sensitivity and Accuracy

- Brain Tumors in General
  - Metastasis
  - Meningioma
  - Status or Activity of M.S.
  - Pituitary Tumors
  - Acoustic Neuroma

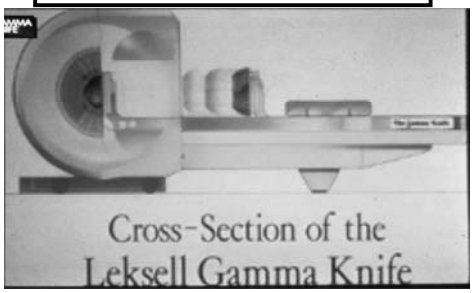
Magnetic Resonance Anglography (MRA)

- Aneurysm
- A/V Malformation
- Occlusive Disease
- Carotid Bifurcation Disease

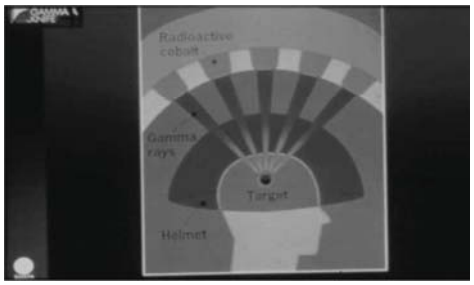
Aneurysm



GAMMA KNIFE



Gamma Knife



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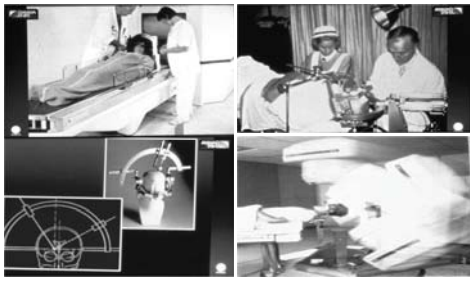

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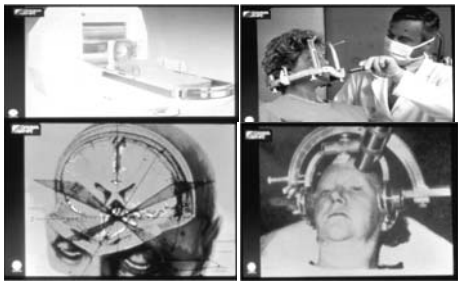
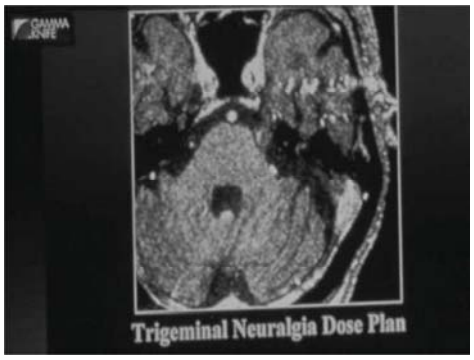
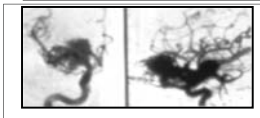




Arteriovenous Malformation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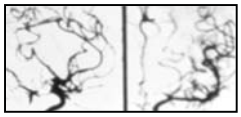
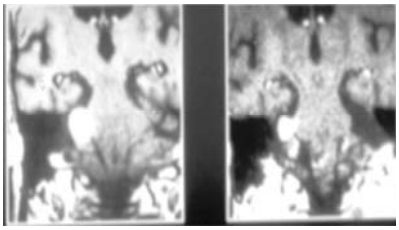
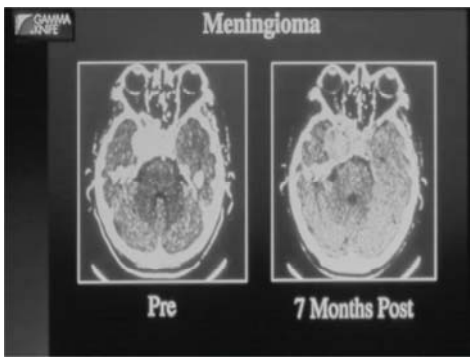
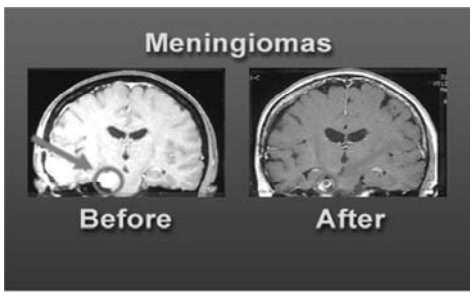

2 Years Post

Acoustic Neuroma


Pre- 24 Months Post





Images demonstrate pre- and post-treatment of Meningiomas Tumor.

Treatment: Recent Study

Type of Tumor	Type of Treatment: Gamma Knife	Conventional Surgery
Acoustic Neuroma:		
Cure Rate	92.0%	97.0%
Cranial Nerve Complications	13.0%	23.0%
Hearing Complications	49.0%	81.0%
Meningiomas:		
Cure Rate	90.0%	67.0%
Complications	.6%	20.0%
A/V Malformation:		
Cure Rate	78.0%	94.0%
Complications	3.1%	11.9%
Metastic Tumor:		
Cure Rate	92.0%	73.0%

RADIATION

- Affects Primarily DNA
- Unit of Measure is Gray (Gy), also Centigray (cGy)
  - Alternate Unit is RAD
  - 1 cGy = 100 RADs
- Average X-Ray = .72 RAD
- Radiation for Primary Brain Tumors - 6000 RAD
  - Fraction: divided radiation dosages (allows normal tissue time to repair)
    - Fractions: 200 qd x 5 days x 5 - 6 weeks
- Radiation for Metastatic Tumors - 3000 RAD
  - Fractions: 200 qd x 5 days x 2 - 3 weeks

RADIATION

- Conventional whole brain radiation causes partial or total hypopituitarism in 1/3 of patients within 2-3 years. Chance increases with patient's age.

SPECIAL THANKS TO:

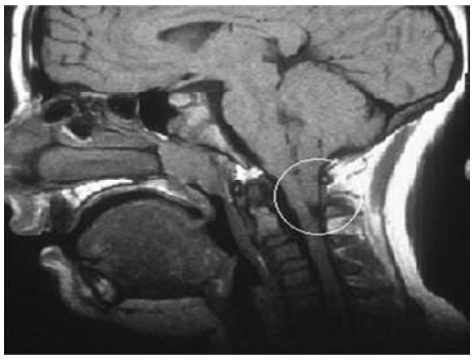
MEGAN TERRY MCMILLAN, CPOA
LECTURE COORDINATOR
FOR DR. DAVID ALLGOOD

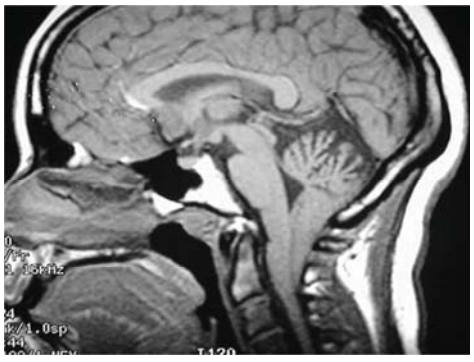
Chiari I Malformation

- 1891: Hans von Chiari first described "hindbrain abnormalities"
- 4 types of Chiari malformations: Types II, III, and IV are distinct from type I
- Type I characterized by herniation of cerebellar tonsils through foramen magnum into cervical spinal canal
- Chiari I is not directly associated with other neuroectodermal abnormalities
- May have a genetic basis

Chiari I Malformation cont.

- May have a genetic basis
- Cerebellar tonsils herniate through the foramen magnum resulting in reduced CSF flow at the craniovertebral junction
- Symptoms:
  - Suboccipital headaches
  - Nystagmus
  - Vertigo
  - Ataxia
  - Cranial nerve palsies
- Dx:
  - MRI Imaging - modality of choice





Fluids of the Central Nervous System

Cerebrosprinal Fluid

A. Function: cushion to the CNS

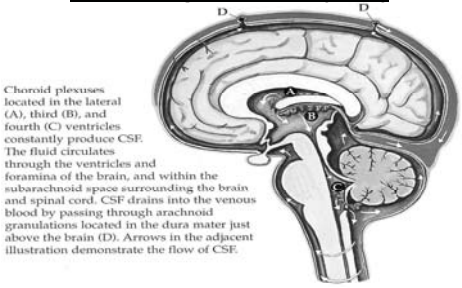
B. Volume: 120-180 ml H2O

C. Production: 600ml most lat.vent and third vent.

D. Flow

E. Lesion Affecting its Distribution

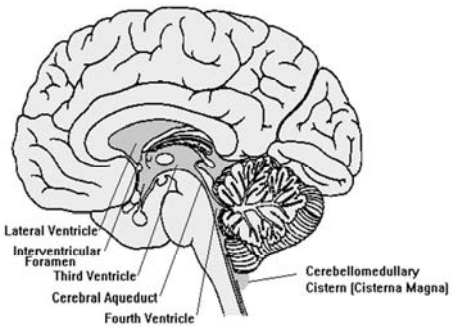
Circulation of Cerebrospinal Fluid (CSF)



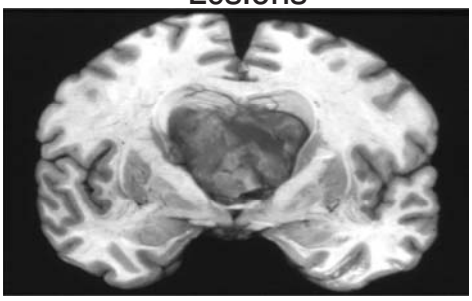
Choroid plexuses located in the lateral (A), third (B), and fourth (C) ventricles constantly produce CSF. The fluid circulates through the ventricles and foramina of the brain, and within the subarachnoid space surrounding the brain and spinal cord. CSF drains into the venous blood by passing through arachnoid granulations located in the dura mater just above the brain (D). Arrows in the adjacent illustration demonstrate the flow of CSF.

COLLOID CYST

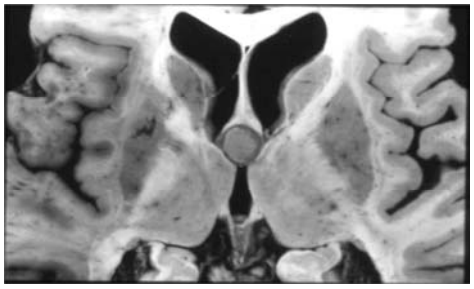
- Composition: Benign tumor of fibrous connective tissue
- Age: 20-55
- Location: Sup./ant. roof of the third ventricle, immediately posterior to the Foramen of Monroe.



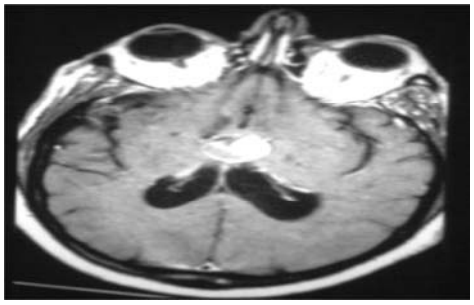
Neoplasms and Related Lesions



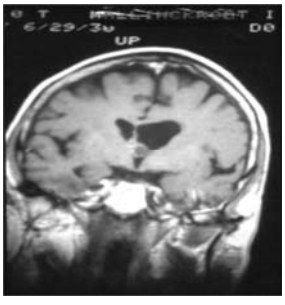
Neoplasms and Related Lesions



COLLOID CYST



COLLOID CYST



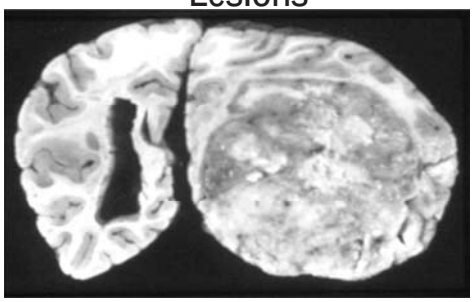
Neuroblastoma

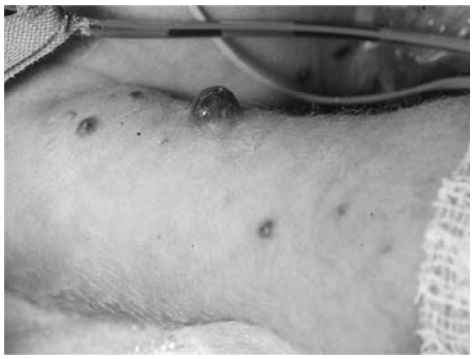
- Tumor of sympathetic nervous system
- Common solid tumor in childhood
- 50% adrenal gland
- Average age is 18 months
- 2/3 of all cases before 5 yrs. of age
- Can be ganglioneuroblastoma (freq. chest) or ganglioneuroma
- Tumor is most often found in children with Opsoclonus-Myoclonus syndrome (OMS)

OMS Syndrome (Kinsbourne Syndrome)

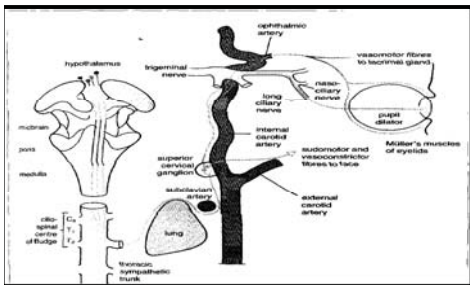
- Nystagmus and muscle jerks and ataxia (incoordination)
- M=F
- Most less than 2 years of age
- Can follow viral infections, (flu), (Epstein-Barr virus 'mono')
- Trouble standing,eating,sleeping,rage attacks,head tilt
- Survival rate is good earlier in age and tumor easier to Tx than syndrome caused by virus
- Tx for those caused by virus is ACTH

Neoplasms and Related Lesions





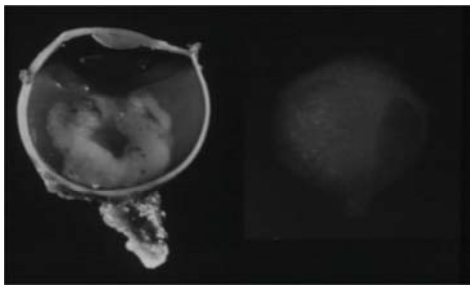
SYMPATHETIC NERVE PATHWAY



Retinoblastoma

- **200 cases per year**
- **2-3 years of age**
- **60-70% are non-hereditary**
- **Metastasis if penetrate choroid (25%)**
- **Familial Cases: Long arm chromosome 13 is susceptibility, predisposed to secondary malignancy (osteosarcoma of femur)**
- **Recurrance:3-4 years initial treatment**

Neoplasms and Related Lesions



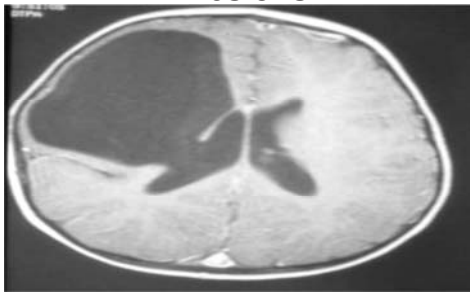
Desmoplastic Infantile Ganglioglioma (DIG)

- **Unusual variant of ganglioglioma**
- **Occurs 1st 2 years of life**
- **Massive, cyptic lesions that displace brain parenchyma**
- **Favorable prognosis with surgery**

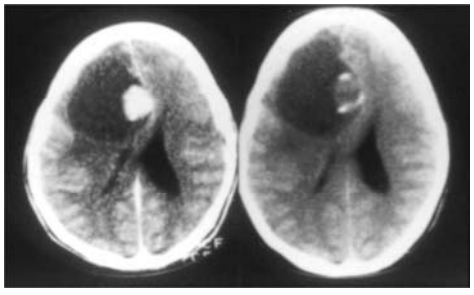
Rare Tumors of Neuronal Origin: Ganglioglioma and Ganglioneuroma Similar Tumors

- **Consist of mature, albeit, neurons**
- **Predisposition for temporal lobes of young subjects (80% in cerebrum)**
- **Favorable prognosis with surgical resection**
- **Often cystic/ focal calcification**

Neoplasms and Related Lesions

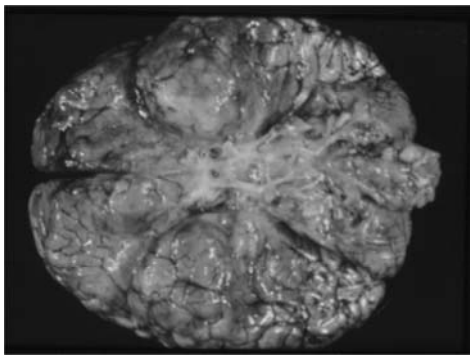


Neoplasms and Related Lesions



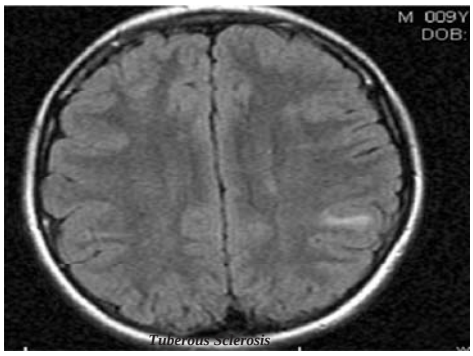
SARCOMAS AND C.N.S.

- Tumors of mesenchymal origin reflect skeletal tissue (bone, cartilage, and connective tissue)
  - i.e. Ewings sarcoma: affects children & young adults. 50% mortality in spite of chemo/radiation/surgery.
- Carcinomas metastasis to CNS > sarcoma due mainly to rarity of sarcoma vs. carcinomas.
- CT: generally do not show presence of inflammatory cells.

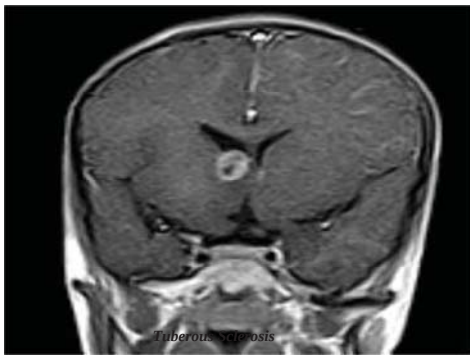


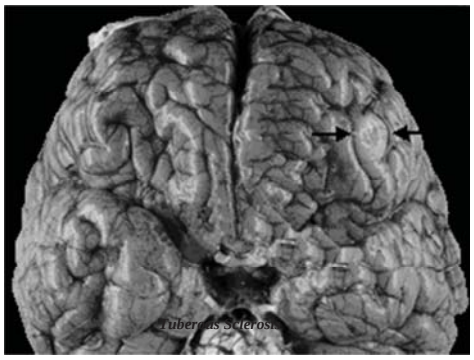
Tuberous Sclerosis

- **Rare complex genetic disorder**
- **Can be inherited or genetic mutation**
- **50% chance for child to have the disease with affected parent**
- **TSC gene 1 on chromosome 9 and TSC gene 2 on chromosome 16 seem to be the problem**
- **Benign tumors of the brain,heart,eyes,lungs,skin**
- **Brain tumors: a. cortical tumors (surface of the brain) b. subependymal (walls of the ventricles) c.giant-cell astrocytomas (alter flow of CSF)**
- **No cure, tx: symptoms**
- **Mild cases in parents can transmit severe cases to children..no set pattern..**
- **CT,MRI,Echo for diagnosis**
- **2 children born everyday with the disease**



Tuberous Sclerosis


Tuberous Sclerosis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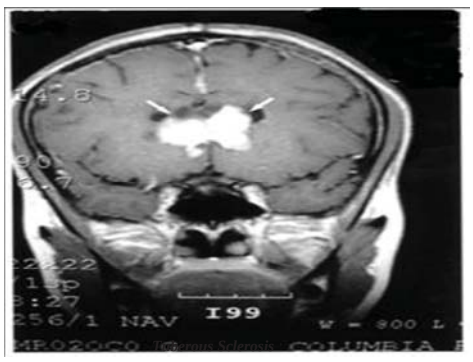
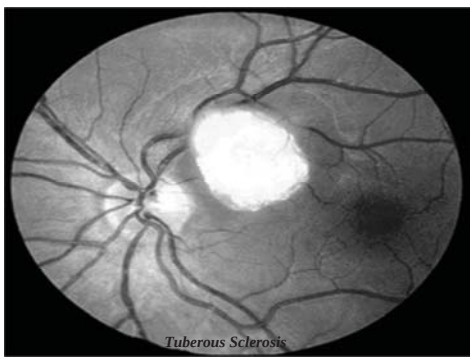


Tuberous Sclerosis


Tuberous Sclerosis

Von Hippel-Lindau

- First described as an angioma of the eye in 1893 by German doctor Von Hippel
- 1 case for every 32,000 people worldwide
- Hereditary disease, alteration in one of the two copy genes referred to as the VHL tumor ‘suppressor gene’ (a long gene susceptible to mutation)

VHL cont.

- Autosomal Dominant Disorder, anyone with a parent with VHL (and most with a brother or sister with VHL) have a 50% risk of the disease
- Has no single primary symptom
- Predisposed to benign and malignant tumors
- Onset of disease is usually between 18-30 years old (Higher incidence occurs with age)
- Often with retinal or cerebellar hemangioblastomas
- In children, especially prone to retinal hemangioblastomas and pheochromocytomas

VHL cont.

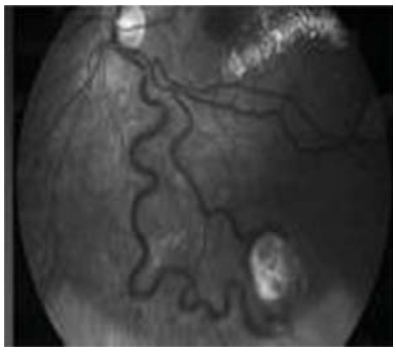
- CNS hemangioblastomas occur in 60-80% (infratentorial 60%)
- Retinal hemangioblastomas, often multiple and bilateral (50%). Most lesions are in peripheral retina but optic discs are 15% of the cases
- Renal cell carcinomas in 75% of cases
- Pancreatic tumors in 75-85% of cases

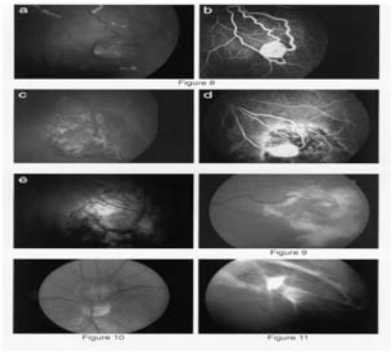
VHL cont.

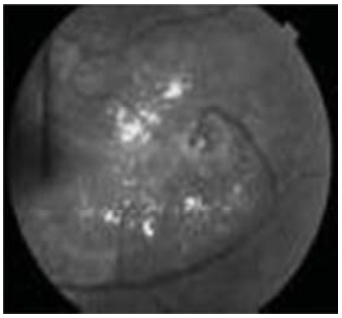
- Detection of affected individuals is by DNA analysis
- Mean of age at death is 50 yrs, with renal cell carcinomas and CNS hemangioblastomas as the major causes of death
- Some early age cancer deaths may actually be attributed to Von Hippel-Lindau Syndrome

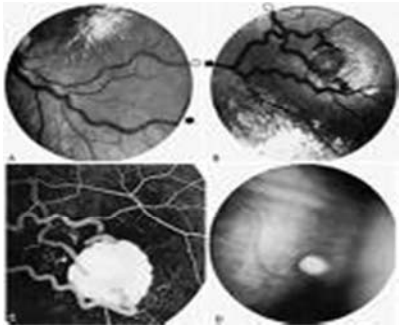
Feud of The Hatfields and McCoys 1878-1891

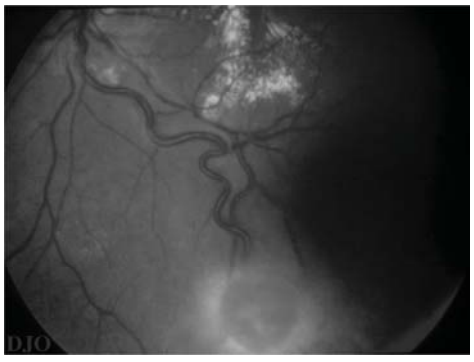
- Both families fought in Civil War (Confederate) of Tug
- Hatfields -West VA./McCoys-Kentucky side Fork Pines River
- VHL can produce 'fight or flight' hormone
- Hair trigger rages
- Dozens of McCoys apparently had the disease
- ¾ of the affected McCoys had pheochromocytomas (tumors of the adrenal gland)
- High levels of nor epinephrine, high blood pressure…led to RAGE attacks











Treatment: Alternative Radiation

- Linear Accelerator
  - Directs arc of radioactive photon beams at the tumor
  - Pattern of arc is computer-matched to the tumor shape
- Cyclotron
  - Adapted nuclear reactor produces particle beams of protons, neutrons or helium ions
  - Used for deep seated tumors such as pituitary tumors

Treatment: Enhancers

- RSR 13
  - Synthetic allosteric modifier of hemoglobin
  - Enhances the release of O2 from hemoglobin making O2 more available by the tissue.
  - Reduces the percentage of hypoxic regions within malignant tumors, therefore enhancing effects of radiation treatment and certain forms of chemotherapy.

Treatment: Chemotherapy

- Monclonal Antibodies (MAB)

New Avenue in Chemotherapy Action:

- Tumor cells have unique proteins (anitgens) on their cell surface.
- Antibodies are produces by WBC and bind only to a specific antigen.
- Therefore antibodies can be used as a 'homing device' to a tumor cell.
- MAB, produced in labs using genetic engineering and cloning techniques, can be use in treatment of brain tumors.
- Could couple antibodies to cytotoxins or radioactive materials to deliver treatment directly to a tumor.

Treatment: Medications

- **Zoloft**
  - **Better than Prozac**
  - **Fewer Side Effects**
- **Antianxiety Drugs: Restoril, Ativan, Serax**
  - **Safest to Use with Cancer Patients**
  - **Only Ones Not Metabolized by Liver**
- **Antipsychotic Drugs: Haidol, Lithium, Tegretol**
  - **Low Does Haldol Helps Bring Thoughts Together**
- **Retalin**
  - **Newest Treatment**
  - **Increases Level of Activity**

Herpes Simplex

Two Types

- H SV-1 Herpes Labialis
- H SV-2 Herpes Genitalis
- Spread by direct mucocutaneous contact.
- Orofacial HSV → 15%- 30% of populating with average 3-4 recurrents a year.
- Incubation period is 3 days to 2wks after exposure.
- HSV is NOT a recurrent disease with latent periods between clinical out breaks.
- HSV is a persistent & chronic infection of the sensory ganglia with a varying , unpredictable degree of skin expression.
- FDA & CDC prefer tests that defect viral glycoprotein –G specific for HSV- 1 (gG1) & HSV- 2 (gG2). The glycoproteins are located on the viral surfaces and viral – infected cells.

Herpes Simplex Serology Test

- Serology testing has limited value in acute clinical diagnoses of patients who develop seropositive ; 65% do so in 6 wks, approximately 20% do not make antibodies for 6 months. Some infected patients never serologically convert.
- Serological negative does not rule out presence of herpes. People display varied immunological responses to HSV. Seropositive patients have been known to shed HSV – 2 viruses on 28% of days tested.

Herpes Simplex Systemic Disease

- HSV is a systemic disease, not only to sensory neurons & dorsal root ganglia but also into epidermal cells, lymphatics and blood. (Virtually all organs)
- Any diseases that causes pain in any organ for 1-2 wks & later recurs in same location might be Herpetic in origin (Bell's Palsy , middle ear infection, proctitis, lumbarsacral H.S)

Herpes Simplex Virus Systemic Disease

- HSV – 2 is largely asymptomatic , most transmissions occur during asymptomatic shedding.
- 70% of HSV – 2 infected patients are completely asymptomatic with no history of overt clinical diseases.
- Acyclovir, valacyclovir, & famciclover are most common agents to treat HSV. All 3 appear to have equivalent clinical efficiencies but none eliminate the virus from the ganglia.
- Oral agents reach peak tissue levels in 1.5 Hrs.

Bimodal Temporal Distributions

- Lips of patients with sun induced HS. Approximately 20-25% develop lesion within 24hrs, the remaining 75-80% have lesions that do not surface until 3-5 days after exposure.
- The immediate peak at one day is from activation of HSV localized soley in epidermal cells, while delayed eruption at 4 days is a result of virus ascending from dorsal root ganglion.
- HSV – 1 & HSV – 2 that are reactivated from dorsal root are easily controlled with oral modalities.
- Reactivation of HSV localized within epidermal cells (occurs 20-25%) is much more recalcitrant to current suppressive oral therapies. These patients respond better to topical antiviral therapy.
- Recurrence rate : patients begin to notice a significant decrease in recurrence seven years after initial infection regardless of treatment.

HSV Advantage

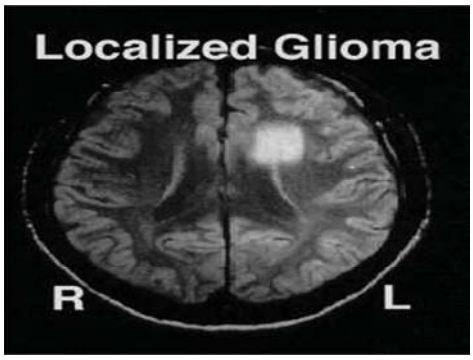
- Evolutionary innovations of cooperative symbiosis among organism.
- HS acts as a pathogen, disease but also benefit to host. It works well with immune system.
- HS appears to offer host oncolytic, immune – stimulating and anti tumor properties.
- Virus hormones thrives in many types of cancer cells and shows selective damage to and initiation of immune response to these cells.

Microglia

- Type of glial cell that are the resident macrophages of the brain and spinal cord
- First and main form of active immune defense in the CNS
- Constitute 20% of the total glial cell population within the brain
- Microglia are distributed in large non-overlapping regions

Microglia (cont.)

- "Immune privileged" organs in that they are separated from the rest of the body by a series of endothelial cells known as the blood-brain barrier, which prevents most infections from reaching the vulnerable nervous tissue
- Where infectious agents are directly introduced to the brain or across the blood-brain barrier, microglial cells must react quickly to ???

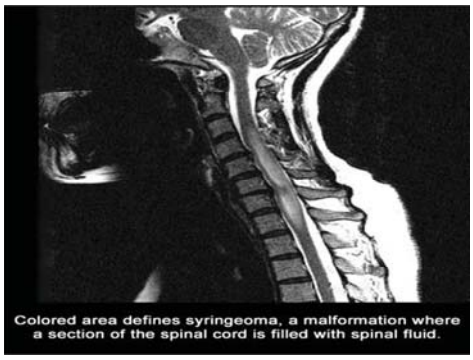


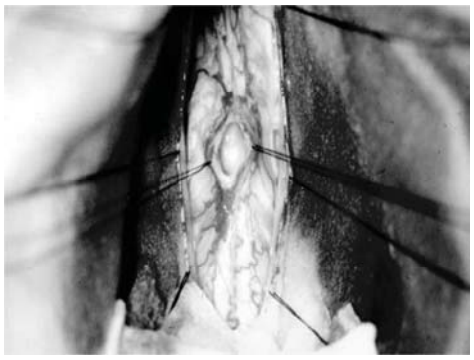
Syringomyelia

- Generic term referring to a disorder in which a cyst or tubular cavity forms within the spinal cord
- Cyst is called a 'syrinx'
- Cyst expands and elongates over time, destroying the center of the spinal cord
- Symptoms are due mostly to interruption of the lateral spinal thalamic tract which passes at the level of the central canal…these fibers conduct pain/temp from dermatomes in upper extremities.

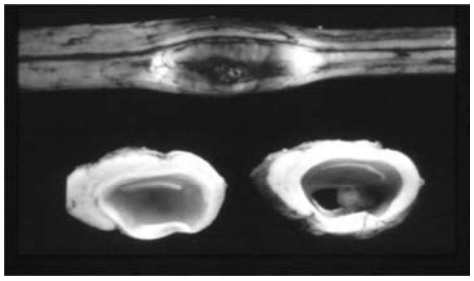
Syringomyelia (symptoms)

- Pain, weakness in upper extremities
- Stiffness in back,neck,arms,or shoulders
- Loss of ability to feel extreme hot or cold
- 'Muzzle' numbness around mouth
- Upper extremity muscle atrophy, especially hands


Colored area defines syringeoma, a malformation where a section of the spinal cord is filled with spinal fluid.



Perinatal CNS Injuries and Congenital Malformations



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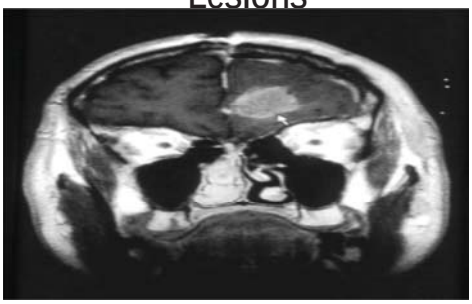


Temporal Lobe and Damage to the Temporal Lobe

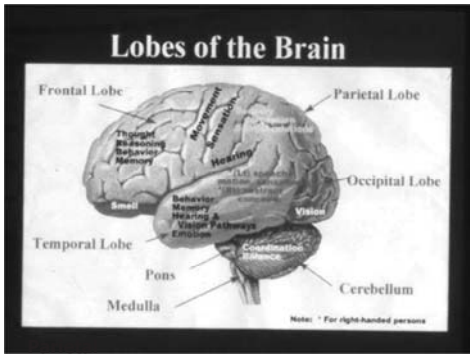
- Disturbance of auditory sensation and perception
- Disturbance of selective attention of auditory and visual input
- Disorders of visual perception
- Impaired organization and categorization of verbal material
- Disturbance of language comprehension

Temporal Lobe & Limbic System (Infection)

- Any CNS inflammatory condition can involve Temporal Lobe.
- Herpes Simplex is one organism with an affinity for the medial Temporal Lobe.
- Most common and gravest form of acute encephalitis with 30-70% rate.
- Almost always type I.H.S. except in neonates where type II predominant symptoms include
  1. Hallucinations, seizures, personality changes and aphasia.

Parietal Lobe

- FUNCTION: interpret visual symbols,
- major sensory stimuli interpretation
- Dominant:
- Anterior: Sensory Agnosia , numbness, tingling (pins/needle) contral., cannot object in hands, cannot recognize by touch, cannot draw no.# on hand.
- Non Dominant: neglect opposite side, decrease in qualities of emotional tone, decrease timing of words, tone/volume of voice inapp.



CEREBELLUM

- Function: Posture, Muscle Tone, Coordination
- Fine voluntary movements (writing, dressing, eating), smooth tracking movements of the eyes.
- Controls property of movements (speed, acceleration, trajectory)
- Not a reflex center in usual sense, it may reinforce some reflexes, inhibit others

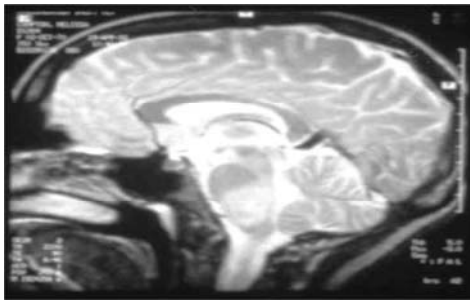
DISSEMINATION OF GLIOMA

- **All forms of gliomas may undergo dissemination : most common is astrocytomas**
- **Favorable sites: meninges, cerebellopontine angle, posterior fossa**
- **Systemic metastasis can occur to lungs, bones, liver, lymph nodes**
- **Most are anaplastic astro or glioblastomas (occasionally oligo)**

Brain Stem Tumor

- ✓**Vomiting -- Awakening**
- ✓**Clumsy, Uncoordinated Walk**
- ✓**VII Palsy**
- ✓**VI Palsy**
- ✓**Difficulty Swallowing, Slurred Speech**
- ✓**Head Tilt**
- ✓**Drowsiness**
- ✓**Very Difficult Tumor to Treat**

Brain Stem no 57



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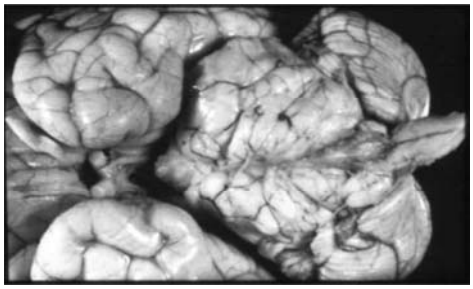

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