Examination?

30.5.
3.6.
6.6.
Neuropsychiatric disorders
Contents

• Stroke
• Epilepsy
• Headache
• Schizophrenia
• Depression
• Multiple sclerosis
• Autism
• Parkinson’s disease
• Alzheimer’s disease
Stroke

• Cerebrovascular accident (cerebrovascular insult, brain attack)
• Transient ischemic attack

= poor blood flow to the brain cause cell death

• Global vs focal

➤ ischemic (poor blood flow)
➤ hemorrhagic (bleeding)
Stroke

- Ischemic 80% (Mortality 20%)
  - thrombosis (50%)
  - embolism (30%)
  - systemic hypoperfusion

- Hemorrhagic 20% (Mortality 80%)
Stroke

- Symptoms
  - face weakness
  - arm weakness
  - speech difficulties
  - vision, smell, taste, hearing impairment
  - headache
Stroke

• Etiology

- blood pressure!
- atherosclerosis
- smoking
- diabetes
- atrial fibrillation
- obesity
- Alcohol consumption
- Drugs (cocaine, amphetamines)
Stroke – animal models

• Endothelin-1 induced vasoconstriction
• Middle cerebral artery occlusion (injecting particles to carotid artery)
• Permanent transcranial middle cerebral artery occlusion
Epilepsy

= group of neurological disorders characterized by recurrent seizures (predisposition 1-3% of population)

= Seizure – abnormal behavior caused by an electrical discharge from neurons in the cerebral cortex

• Partial seizures (Simple partial, Complex partial, secondary generalized)
• Generalized seizures (absence, atonic, tonic, clonic, tonic-clonic)

• Etiology: unknown... brain injury, stroke, brain tumors, infections, birth defects
Epilepsy

• **Partial seizures**
  - **simple partial** (consciousness, symptoms on the cont.side, motor or sensory, ANS – hypo or hypertension, tachycardia, sweating may occur)
  
  - **complex partial** (impaired consciousness, from temporal lobe/psychomotor seizures, automatism – repetitive, non-purposeful actions – lips smacking, grimacing, patting, rubbing clothes. Postictal confusion – hallucination, dé déjà, jamais vu)
  
  - **secondarily generalized partial** (progression to tonic-clonic seizure activity)

  - Aura
Epilepsy

• **Generalized seizures**
  - **Absence** (disturbance in consciousness; blank stare, motionless, unresponsibility)
  - **Atonic** (slackening of the jaw, drooping of limbs, falling to the ground, „drop attacks“)
  - **Tonic**
  - **Clonic**
  - **Tonic-clonic**
Animal models

• Models of epileptic seizures rather than epilepsy
• Maximal electroshock seizure
• pentylentetrazole
• Kindling
Headache

- **Pain** is a distressing feeling often caused by intense or damaging stimuli.
- Brain lacks pain receptors
- Several areas of head and neck do have pain receptors:
  - Extracranial arteries, middle meningeal artery, large veins, venous sinuses, cranial and spinal nerves, head and neck muscles, eyes, ears, teeth and lining of the mouth
Headache

• secondary vs primary (90%)

• Tension-type headache
• Migraine
• Cluster headache
• Chronic daily headache
• Headache attributed to... Head/neck trauma, cranial disorder, nonvascular intracranial disorder, substance or its withdrawal,
Headache

**Tension type headache**

- most common type
- Usually not sufficiently severe to interact with daily activities
- Dull, aching, diffuse, nondescript, hatband distribution
- Infrequent, episodic or chronic
- Unknown cause – theory: sustained tension of the muscles of the scalp and neck; psychogenic stress, anxiety, depression, muscular stress, overuse of analgesics or caffeine overuse (or lack of caffeine in addicts 😊)
- More responsible to non pharmacologic techniques
Headache

Migraine

• Without aura (85%)
  ➢ pulsatile, throbbing unilateral headache, 1-2 days, nausea & vomiting, sensitivity to light & sound, visual disturbances

• With aura (15%)
  ➢ similar but + visual or neurologic symptoms that precede the headache

• Gender differences in occurrence
Headache

Migraine

• Etiology (AD with uncomplete penetrance, estrogens...)

• Management
  ➢ Non-pharmacological
  ➢ Pharmacological
Headache

**Chronic daily headache**

- 15 or more days a month
- Unknown cause, theories:
  - transformed migraine headache, new daily persistent headache, postraumatic headache

- Manifestations: from migraine to chronic tension-like headache

- Treatment: combination of pharmacologic and behavioral interventions
Headache

**Cluster headache**

- Relatively uncommon
- Occur in clusters over weeks or months followed by a long, headache free remission phase
- Primary neurovascular headache with rapid onset (duration 15-180 min)
- Severe unrelented unilateral pain located in orbital, retroorbital, temporal, supraorbital and infraorbital region
- More common in men
- Treatment: quickly acting medications
Cluster: pain is in and around one eye

Tension: pain is like a band squeezing the head

Migraine: pain, nausea and visual changes are typical of classic form
Headache – animal models

• Activation of pain-producing cranial structures
• Trigeminal autonomic cephalalgias...
Schizophrenia

- Mental disorder characterized by abnormal social behavior and failure to understand reality
- Disorder or thought and language
- Not! “multiple personality disorder“
Schizophrenia

Symptoms

- Positive
  - Disorganized, incomprehensible speech
  - Delusion
  - Hallucinations (mostly auditory)
  - Disorganized behavior
  - Impaired ability to respond to environment
  - Enhancement or blunting of senses in the early stage

- Negative
  - Alogia
  - Avolition (lack of motivation)
  - Apathy
  - Affective flattening
  - Anhedonia
Schizophrenia

**Paranoid schizophrenia**
- Persecutory or grandiose delusions
- Auditory hallucinations
- Negative symptoms not prominent
- Better prognosis, less disturbance in brain anatomy

**Disorganized schizophrenia**
- Disintegration of personality
- Predominance of negative symptoms
- Socially withdrawn and inept
- Personal grooming neglected
- Daily activities disturbed
- Prognosis not good

**Catatonic schizophrenia**
- Rare
- Psychomotor disturbance (retardation or excitement)
- Extreme negativism
- Peculiar voluntary movements (grimacing, posuring, echolalia or echopraxia)
Schizophrenia

- **Etiology**
- Unknown
  - Abnormalities in brain anatomy at the onset
  - Combination of environmental and genetic factors
  - Environmental factors: being raised in a city, cannabis use, parental age, poor nutrition during pregnancy, certain infections
  - High rate of substance abuse

  - Dopamine hypothesis: mind’s faulty interpretation of the misfiring of dopaminergic neurons (increased dopamine receptors)
Schizophrenia

**Diagnostic criteria**

- At least **two** of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior must be present.

**Treatment**

- Goals: Induce remission, prevent recurrence, restore behavior, cognitive or psychosocial functions
- Pharmacological & non-pharmacological
Schizophrenia – animal models

• Developmental
• Drug – induced (amphetamine), DA receptor agonists
• Lesion
• Genetic manipulation
Depression

• Mood disorder
• Disorder of emotions rather than a disturbance of thought
• Common & underdiagnosed & undertreated
• 20% of population
  ➢ unipolar (persistent unpleasant mood) F>M
  ➢ bipolar (alternating periods of depressions and mania) F=M
  ➢ seasonal affective disorder (SAD)

• Etiology – genetic predisposition, ↓ serotonin and norepinephrine, reduction of gray matter in the prefrontal cortex (probably important for mood control and connected to limbic sy), frontal and temporal lobes - ↓ function, amygdala - ↑ blood flow and oxygen consumption, cortisol spikes over 24h d.
Depression

**Manifestations**
- Depressed mood
- Anhedonia
- Feeling of worthlessness or excessive guilt
- Decreased concentration
- Psychomotor agitation or retardation
- Insomnia or hypersomnia
- Decreased libido
- Change in weight or appetite
- Thoughts of death or suicidal ideation
Depression

**Unipolar depression**

- **melancholic** - worse in the morning, insomnia with early morning awakening, anorexia with significant weight loss, psychomotor retardation or agitation, excessive or inappropriate guilt, loss of interest in activity, inability to respond to pleasurable stimuli, and a complete loss of capacity for joy.

- **atypical** - becomes worse as the day progresses, overeating, and hypersomnia (excessive sleep).

- **depression with psychotic features** - presence of delusions or hallucinations that may or may not be mood congruent

- **depression with catatonic features** - excessive mobility or motoric immobility, extreme negativism, repetitive speech, and peculiar voluntary movements

- Chronic specifier is applied if symptoms persist more than 2 years
Depression

Bipolar depression

- Manic – depressive illness
- characterized by periods of elation or irritability (mania) with or without (unipolar mania) episodes of depression.
- Unipolar mania is rare
- Manifestations of mania: decreased need for food and sleep, labile mood, irritability, racing thoughts, high distractibility, rapid and pressured speech, inflated self-esteem, and excessive involvement with pleasurable activities, some of which may be high risk.

- subjective experience of mania can be quite pleasurable to the individual, with a heightened sense of wellbeing and increased alertness

- Rapid cycling – four or more mood shifts during 1 year
Depression

Diagnostic criteria

• Simultaneous presence of five or more aforementioned symptoms during a 2-week period and these must represent a change of previous functioning

• Must be differentiated from grief reactions, medication side effects and sequelae of medical illnesses.

• Bipolar - basis of the pattern of occurrence of manic, hypomanic, and depressed episodes over time that are not due to medications or other therapies.
Depression

Treatment

• antidepressant drugs, electroconvulsive therapy, lithium, anticonvulsants, and psychotherapy

• psychotherapy
Depression – animal models

• Olfactory bulbectomy model
• KOs: melatonin receptor, α-adrenergic receptor, aromatase receptor, thyroid hormone receptor....
Multiple sclerosis

• Demyelinating disease of CNS
• Demyelination of neurons in the white matter of the brain, spinal cord and optic nerve => conduction abnormality
• Destruction by immune sy or fail to produce myelin
• The most common non-traumatic neuro disability
• First symptoms 20-40 years, F>M
• Exacerbations and remissions (80%)
• Immune mediated disorder that occurs in genetically susceptible individuals
• Initiation process?

Demyelinated or sclerotic patches
Multiple sclerosis

Symptoms

**Early Symptoms of MS**
- Blurred or double vision.
- Thinking problems.
- Clumsiness or a lack of coordination.
- Loss of balance.
- Numbness.
- Tingling.
- Weakness in an arm or leg.

**MS Relapse Symptoms**
- Memory or thinking problems
- Vision changes
- Speech changes
- Chewing/swallowing
- Hand/arm weakness
- Bladder or bowel problems
- Difficulty walking
- Leg/foot weakness
- Whole body:
  - Fatigue
  - Coordination
  - Dizziness/poor balance
  - Muscle tightness or stiffness
  - Numbness/tingling
  - Pain
  - Burning
  - Itching
Multiple sclerosis

**Treatment/medications**

- to treat acute symptoms of the disease,
- those used to modify the course of the disease,
- those used to interrupt progressive disease, and
- those used to treat the symptoms of the disorder.

- Anti-inflammatory, immunosuppressants
Multiple sclerosis – animal models

- Myelin basic protein mutant
- Proteolipid protein mutant
- Myelin associated protein mutant

- Murine encephalomyelitis virus

- Experimental allergic encephalomyelitis
Autism

• Autism spectrum disorders (ASD)
• Presence of abnormal or impaired development
• Onset of symptoms: before 3 years of age
• $\mathcal{M} : \mathcal{W} = 2.5 - 4:1$

Triade of symptoms:

- impaired social interaction
- impaired social communication
- repetitive (stereotyped) behavior

Specific cause still unknown
Autism - prevalence

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Autism – social deficits

- Lack of non-verbal behavior (eye-to-eye gaze, facial expression, gestures, body postures)
- Lack of appropriate peer relationships
- Absence of social-emotional reciprocity
- Less eye contact
- Less interest in human voices and faces
- Lack of strong emotional relationships to mothers
- Frequent absence of responding to own name
- Less interest in social interaction or social stimuli
- Less interest in social play with peers
Autism – social deficits

Inappropriate playing with toys
Poor speech or lack of speech
Lack of eye contact
Hyperactivity or Passiveness

Inability to relate to children or adults

Inability to relate to others

Oversensitive or undersensitive to touch
Autism – testosterone?

- **Extreme Male Brain Theory**: autism as an extreme manifestation of some sexually dimorphic traits
- **Testosterone, 2D:4D & Autism**:  
  - males have lower 2D:4D ratio than females  
  - **De Bruin (2006)**: males with ASD have lower 2D:4D ratio than unaffected individuals  
  - **Manning (2001)**: siblings and parents of autistic individuals have lower 2D:4D than
Autism – animal models

• Prenatal testosterone 😊
• Neuroglin mutants
• Oxytocin receptor mutants
Parkinson’s disease

- Degenerative disorder of the CNS, mainly affecting the motor system
- Degradation of dopaminergic neurons in substantia nigra
- Primary vs secondary

Cut section of the midbrain where a portion of the substantia nigra is visible

Substantia nigra

Diminished substantia nigra as seen in Parkinson’s disease

Dopamine levels in a normal and a Parkinson’s affected neuron.

Normal Neuron
- Normal movement

Movement disorders

Lewy bodies
Parkinson’s disease

**Symptoms**

- shaking
- rigidity
- bradykinesia
- postural instability

Later: dementia, depression
Parkinson’s disease

- **Treatment**
  - dopamine agonists (early)
  - L-DOPA

- **Etiology**
  - cause?
  - pesticides?
  - Tobacco smoke protective?
Parkinson’s disease – animal models

• Reserpine
• 6-hydroxydopamine
Alzheimer’s disease

- Inherited vs sporadic
- Short-term memory loss (Pre-dementia)
- Aphasia, Apraxia, Agnosia (Early)
- Hindered independence, paraphasias, long-term memory impairment (Moderate)
- Completely dependent upon caregivers, apathy, exhaustion (Advanced)

- Neuritic plaques
- Tau protein
Alzheimer’s disease

• **Pathophysiology**
  - inherited: AD mutations in amyloid precursor protein (APP) or presenilins 1 and 2
  - sporadic –
    - risk factors: mutations in apolipoprotein E
    - Cholinergic hypothesis
    - Amyloid hypothesis
    - Tau hypothesis (hyperphosphorylated tau – neurofibrillary tangles)
Alzheimer’s disease

• Other hypothesis
  ➢ Viruses, prions, zinc
  ➢ trauma
  ➢ low level of education
Alzheimer’s disease

- Neuropathology
Alzheimer’s disease - scopalamine

• Scopalamine
• Infusion of αβ-peptides into brain
• APP mutants