

## NEUROBIOLOGY OF PSYCHIATRIC DISORDERS

Advanced Pathophysiology

Prof. Brown-Kishbaugh MSN, FNP-C, APRN

### Starting points

- Every mental d/o manifests with varying severity and at times difficult to diagnose.
- Understanding the neurobiology can guide treatment and aid in lessening the severity of the disease process.
- MENTAL ILLNESS INTERACTS WITH CHRONIC DISEASE PROCESS AND IMPACTS DAILY LIVING

### Neurotransmitters (inhibitory/excitatory)

- Acetylcholine
- Amines-
  - Serotonin
  - Histamine
  - Dopamine
  - Epinephrine
  - Norepinephrine
- Amino acids
  - Glutamate
  - Gaba (gamma-aminobutyric acid)
  - Glycine
- Neuropeptides
  - Substance P
  - Enkephalins

- Endorphins

## Schizophrenia

- DEFINITION
  - Serious psyche illness <1% of world's population
  - Emerges late teen, young adults
  - Male (<25) >female (<35)
  - "thought disorder" reflect a break in reality or splitting of of the cognition side from the emotional side
- ETIOLOGY
  - Inheritable; multifactorial (stress diathesis)
  - Multiple theories on pathway development but not completely understood
  - Characterized as having at least 2 of the following:
    - hallucinations, delusions, disorganized speech, disorganized/catatonic behavior, or negative symptoms
- PATHOPHYSIOLOGY THEORIES
  - Identifiable underlying structural and functional brain abnormalities
  - Stress diathesis
    - includes specific vulnerability that gets re-exposed over time and leads to development of schizo
  - neuroanatomical differences
    - have been found in brain imaging studies carried out during the at-risk period
  - abnormalities is an imbalance between neurotransmitters
    - Dopamine
    - Glutamate
    - Excitotoxicity
    - excessive stimulation of glutamate neurons at the hippocampus leads to their toxicity and eventual degeneration
- DIAGNOSIS
  - no pathognomonic features and no confirmatory laboratory tests.
  - positive symptoms (auditory hallucinations, thought disorder, delusions)
  - negative symptoms (demotivation, self-neglect, and reduced emotion)
  - For a diagnosis, at least one of the following symptoms must be present: delusions, hallucinations, or disorganized speech.
- EPIDEMIOLOGY

- Inheritable
- age of onset is usually <25 years for males and <35 years for females
- higher disease incidence in urban and low-income populations when compared with rural and higher-income groups
- Suicidal tendency >> up to 15% of schizophrenics may kill themselves.
- Highest risk at the onset

**Mood D/O: Depression and Bipolar**

Mood

- Sustained emotional state as opposed to a brief emotional state of feelings, termed affective states
- Healthy individuals are able to maintain a variety
- Fear, sadness, anxiety depression, euphoria, joy and surprise
- When emotional states become chronic and uncontrollable, may progress to depression
- characterized by persistent loss of interest and enjoyment and low mood; neurovegetative disturbance, and reduced energy
- Can cause varying levels of social and occupational dysfunction

Types

<p>Unipolar</p> <ul style="list-style-type: none"> <li>▪ Major depressive DO</li> <li>▪ Persistent depressive DO</li> <li>▪ Dysthymic disorder</li> <li>▪ Premenstrual dysphoric disorder</li> <li>▪ Other               <ul style="list-style-type: none"> <li>○ Med ADRs</li> <li>○ Substance abuse</li> </ul> </li> </ul>	<p>Bipolar</p> <ul style="list-style-type: none"> <li>▪ Bipolar I</li> <li>▪ Bipolar II</li> <li>▪ Cyclothymic disorder</li> <li>▪ Other specified bipolar disorder</li> </ul>
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Unipolar depression

- Definition
  - multiple chronic depression forms in which depressive sx "more days than not"
  - over at least a 2-year period
  - 1 year in children and adolescents
  - 2nd leading cause of disability overall
- Etiology
  - Poorly understood
  - Genetics (no gene identified)
  - biologic and social variables
  - Stressful life events

- Women 2x >men

## Pathophysiology of depression

### Neurochemical dysregulation

- serotonin and noradrenergic systems and dopamine (DA)
- monoamine oxidase
- enzyme responsible for the oxidative deamination of neurotransmitters such as serotonin, norepinephrine, and dopamine
- Depressed or reduced levels of Monoamine levels resulted in depressed states whereas elevated levels resulted in hypermanic states

### Neuroanatomic

- brain imaging studies have evidence of :
- widespread decrease in 5HT serotonin receptor subtype in frontal, temporal and limbic cortex
- Possible dysfunctional raphe-serotonin system
- Frontal and limbic structural and functional abnormalities
- Decreased cerebral blood flow and glucose metabolism
- Enlarged ventricles

### Neurochemical dysregulation

- enzyme MAO comes in two forms ☐ MAOa and MAOb
- MAOb metabolizes phenylethylamine + MAOa, breaks down dopamine
- MAOa = breakdown of serotonin and norepinephrine
- Tyramine is usually metabolized in the gastrointestinal tract, but the blockade of MAOa allows it to flow into the general circulation

### Neuroendocrine

- H-P-A axis = cope with stressors☐ there is chronically elevated cortisol levels
- Chronic activation of this and excessive glucocorticoid secretion are found in 30-70% of pts w/ major depressive do
- Also increased stress activate inflammatory cascade (pro-inflammatory il-6, tnf-a, interleukin 1 alpha and beta ☐ further augments HPA hormones and monoamines)
- H-P-T axis dysregulation
- 20-30% have increased levels of thyrotropin releasing hormones , a blunted TSH response and decreased nocturnal elevations. This is associated with relapse

### Depression Clinical manifestations

- poor appetite or overeating
- insomnia or hypersomnia
- low energy or fatigue
- low self-esteem
- poor concentration or difficulty making decisions
- feelings of hopelessness.

### Diagnostics

- Patient health questionnaire (PHQ-9)
- Beck Depressive Inventory (BDI)
- Quick Inventory of Depressive Symptoms (QIDS)
- Primary care evaluation of mental disorders (PRIME-MD)
- Mood Disorder questionnaire (MDQ)
- CBC, TSH, Vit D, toxicology screen

## Bipolar

### Definition

- Psyche illness characterized by alternating periods of abnormal mood elevation and depression associated with a change or impairment in functioning
- alternating mood elevation (mania or hypomania) and depression
- Etiology exact cause is unknown
  - Genes, environmental stressors and triggers contributing to phenotypical expression

### Types

- Bipolar I
  - At least 1 manic or mixed episode
  - Usually treated w/ lithium (control mania, reduced SI & rapid cycling)
- Bipolar II
  - Never had a full manic episode
  - at least 1 hypomanic episode and at least 1 major depressive episode
  - SSRI and SNRI

### Patho (in addition to depression)

- increased periventricular white matter hyper intensities
- prefrontal cortex is of particular interest
- difficulties with the regulation of emotional expression (such as inappropriate or labile affect) and behavior (such as impulsivity or sexually inappropriate behaviors)

- existence of alterations in patients' ability to identify and to generate emotionally salient information and experience on a neurophysiologic basis
- Alteration of N-acetyl aspartate, choline, myoinositol, glutamate, and other critical substrates involved in regulation of mood.

#### Clinical presentation

- predominance of depression
- history of at least one manic, hypomanic, or mixed episode
- is required to make the diagnosis of a bipolar disorder.
- Hypomania = elevated states without significant functional
- characterized by abnormally elevated or irritable mood episode
- + disruptive symptoms of distractibility, indiscretions, grandiosity, flight of ideas, hyperactivity, decreased need for sleep, and talkativeness

#### Diagnostics

- Patient health questionnaire (PHQ-9)
- Beck Depressive Inventory (BDI)
- Quick Inventory of Depressive Symptoms (QIDS)
- Primary care evaluation of mental disorders (PRIME-MD)
- Mood Disorder questionnaire (MDQ)
- Bipolarity index (>60)
- CBC, TSH, Vit D, toxicology screen

#### Anxiety disorders

- Include generalized Anxiety d/o, Panic attacks, PTSD and OCD
- Most prevalent psychiatric Dx ☐ 10-30% of population
- Many anxiety and depression co-morbid correlations leading to believe neuronal pathways are similar

#### Generalized anxiety d/o

##### Definition

- Chronic condition of excessive worry
- >6 months
- everyday issues that is disproportionate to any inherent risk
- causing distress or impairment

##### Etiology/epidemiology

- no single etiology but all seem to contribute
- an increase in minor life stressors
- presence of physical or emotional trauma
- genetic factors

- prevalence of 7.8% (lifetime)
- prevalence of 4% (1-year)
- in the US
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#### Anxiety patho

- abnormal responses to stress
- multiple neurotransmitter involvement
- neurohormone alterations
- sleep disturbances
- chromosomal and genetic factors.

#### Clinical presentation

- At least 3 key symptoms out of a possible 6 are required to make a diagnosis:
  - restlessness or nervousness, easy fatigability
  - poor concentration, irritability, muscle tension
  - sleep disturbance.

#### Diagnostics

- a diagnosis of exclusion
- medical conditions
- medications or substance
- other mental disorders
- should be ruled out
- TSH, drug screen

### Panic disorder

#### Definition

- recurring expected or unexpected panic attacks
- worry about future attacks over a 1-month period
- changes in behavior as a consequence of the attacks.

#### Etiology/epidemiology

- Genetics, environmental and psyche factors predispose to developing
- 8-28% of individuals experience panic attacks at some time during their life
- Native Am>>Cauc >>Asian, Latinx, AA

#### Panic patho

- involvement of the central nuclei of the amygdala
- activation of other fear centers of the brain, such as the thalamus, hypothalamus, and hippocampus
- may dysregulate respiratory control in the brainstem
- exaggerated hypothalamic-pituitary-adrenal axis
- reactivity to environmental stimuli may be involved in panic disorder

### Clinical presentation

- recurring expected or unexpected panic attacks
- worry about future attacks over a 1-month period
- changes in behavior
- Intense autonomic arousal
- tachycardia, diaphoresis, lightheadedness, difficulty breathing
- chest discomfort, weakness, trembling, abdominal distress and chills/hot flashes

### Diagnostics

- Panic symptoms can NOT be caused by :
  - substance-related effects (withdrawal, medication side effects)
  - medical conditions (hyperthyroidism, menopause)
  - other psychiatric disorders such as specific phobias, obsessive compulsive disorder
- TSH, Tox, ECG, glucose

### Posttraumatic stress disorder (PTSD)

#### Definition

- Immediate or delayed disorder following exposure to a stressful event or situation of an exceptionally threatening or catastrophic nature
- 4 groups of symptoms and must impair function for DX
  - intrusion symptoms
  - avoidance
  - negative alterations in cognition/mood
  - alterations in arousal and reactivity.
- OFTEN comorbid w/ depression, anxiety, anger, and substance misuse.

#### Etiology/epidemiology

- Psyche and neurobiological theories
- Traumatic events
  - threats to their own life or the life of others while in medical care
  - such as during anesthesia
  - complications during childbirth
- medical negligence
- Epidemiology varies greatly between countries
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#### PTSD patho

- Hyper-reactivity to threat, oversensitive negative feedback system w/ cortisol
- Lower than normal levels of cortisol inhibit production of ACTH from the anterior pituitary gland, and there is evidence of downregulated sensitivity to corticotropin-releasing-factor (CRF) resulting in suboptimal levels of cortisol
- neurochemicals



- serotonin, gamma-aminobutyric acid, glutamate, neuropeptide-Y, and brain-derived neurotrophic factor.
- neurobiology of PTSD is complex and involves a range of these and other factors

#### Clinical presentation

- Exposure to trauma
- Intrusive sx
- Avoidance sx
- Negative alterations in mood and cognition
- Alterations in arousal and reactivity

#### Diagnostics

- TSQ (Trauma screening questionnaire)
- PTSD Diagnostic Scale (PDS-%)
- PTSD Checklist for DSM5
- ITQ (International Trauma Questionnaire)

#### Obsessive-Compulsive D/o

##### Definition

- Psyche disorder in which obsessions and/or compulsions cause marked distress
- >1 hour/day
- interfere substantially with the person's normal routine, occupational or academic functioning
- or usual social activities or relationships
- average amount of time that lapses between onset of symptoms and appropriate treatment is 17 years.

##### Etiology/epidemiology

- Genetic factors (AD pattern)
- Learning theories, cognitive theory; rarely head trauma or striatal lesions
- Affects 1-4% world
- Ages 15-44
- women =men
- Cultural specificity
- US, Canada, PR, Germ, Korea, New Zeal
- low prevalence

##### OCD patho

- Evidence of autosomal dominate transfer
- serotonergic dysfunction plays a role in the pathophysiology of OCD
- Low prolactin response to meta-chlorophenylpiperazine (m-CPP) serotonin stimulation has been implicated as a predictor of poor response to selective serotonin-reuptake inhibitors

- a hypermetabolic brain circuit involving the orbital-frontal cortex, anterior cingulate, thalamus, and striatum

#### Clinical presentation

- obsessions
  - unwanted, disturbing, and intrusive thoughts, images, or impulses
  - generally seen by the patient as excessive, irrational, and ego-alien
- compulsions
  - repetitive behaviors and mental acts that neutralize obsessions and reduce emotional distress

#### Diagnostics

- Clinical diagnosis
- Structured clinical interview for the DSM (SCID)
- Yale-Brown OCD scale
- CGI (clinical global impression)

#### References

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UP TO DATE various topics

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