### NEUROPSYCHOLOGICAL CHANGES FOLLOWING CUSHING'S: TEMPORARY AND PERMANENT?

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### GOALS OF THE TALK

- Explain role of cortisol in neuropsychological problems associated with Cushing's.
- Discuss current research findings regarding temporary and long-term cognitive and psychological problems with Cushing's.
- Discuss specific findings from the Emory clinical Cushing's population.
- Next steps?

#### HUMAN NERVOUS SYSTEM

- Central Nervous System (CNS) Brain and Spinal Cord
- Peripheral Nervous System (PNS)
  - Somatic Nervous System Voluntary Movement
  - Autonomic Nervous System Involuntary Activities
    - Sympathetic Nervous System "Fight or Flight"
    - Parasympathetic Nervous System "Rest and Digest"

#### SYMPATHETIC AND PARASYMPATHETIC NERVOUS

#### SYSTEM



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### THE SNS AND PSNS WORK TOGETHER TO PROMOTE HOMEOSTASIS



Rest-and-digest: Fight-or-flight: Parasympathetic Sympathetic activity activity dominates. dominates.

Elevine dd d

## WHAT HAPPENS WHEN WE ENCOUNTER A STRESSOR?

Stress triggers the response of the hypothalamicpituitary-adrenal axis, a neuroendocrine system.

This sets off a cascade of signals that ultimately leads to the release of hormones and neurotransmitters like cortisol, norepinephrine (noradrenaline), and epinephrine (adrenaline).

#### THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS





### CORTISOL- THE "STRESS HORMONE"

Cortisol is the main hormonal mediator of stress in humans.

 Cortisol secretion results in behavioral changes of increased vigilance, alertness and attention that allow ability to cope with stress.

Prolonged cortisol excess leads to physical and behavioral abnormalities, as does chronic secretion of cortisol.

### CUSHING'S SYNDROME- THE EXTREME EXAMPLE

- Cushing's syndrome is characterized by elevated levels of serum cortisol that occur usually as a result of a pituitary tumor that produces excessive ACTH, or by chronic use of high levels of medications that mimic cortisol (e.g. steroids).
- Symptoms include:
- Central weight gain
- Striae/severe stretch marks
- Muscle weakness
- Changes in hair distribution
- Mood lability/irritability

- Easy bruising
- "Moon faces"
- High blood pressure
- Changes in sex hormones

#### **Panic symptoms**

Difficulty with concentration and memory

# EFFECTS OF CHRONIC CORTISOL SECRETION ON THE BRAIN: PSYCHOLOGICAL SYMPTOMS

Psychological disorders are common in Cushing's, both due to the hypersecretion of cortisol, and the distress patients feel due to the physical changes in their bodies.

- Most common disorders include:
  - Depression (66-90% incidence)
  - Anxiety and panic disorder
  - Mania (less common)

## WHY IS CORTISOL IMPLICATED IN PSYCHOLOGICAL DISORDERS?

Cortisol abnormalities, notably the dysregulation of the HPA Axis has been seen in individuals with depression.

Depression is induced when individuals are given synthetic glucocorticoids for other disorders (e.g. immunosuppression).

### THE GOOD NEWS

- Treatments by surgery or medications resulted in a significant decrease in depression scores. (Dorn, et al. 1997, Flitsch, Spitzner and Ludecke 2000).
- Postoperatively, progressive improvement of the depression scores was found at 3, 6 and 12 months postoperatively(Dorn et al, 1997).
- One year after cortisol levels returned to normal, the rates of major depression and anxiety dropped to 24%

### HOWEVER...

- Depression remained the prevailing psychiatric diagnosis along with an increase in suicidal ideation and panic disorder, even years after surgery (Dorn et al, 1997).
- This has been replicated in other studies, with patients anecdotally reporting persisting cognitive and psychiatric complaints affecting quality of life despite improved cortisol status (Pereira et al 2012).

### THE QUESTION REMAINS...

Are these symptoms of depression and anxiety secondary to changes in brain structure or function due to the hypersecretion of cortisol?

Or is this emotional distress due to changes in quality of life following Cushing's? Or some combination of the two?

Or a third, unstudied option- do people develop a maladaptive somatic focus after Cushing's that contributes to the maintenance of depression or anxiety?

### EFFECTS OF CHRONIC CORTISOL SECRETION ON THE BRAIN: COGNITIVE SYMPTOMS

In addition to abnormalities in emotional functioning with Cushing's syndrome, individuals with Cushing's syndrome also report a decline in cognitive functioning.

 Specific areas of impairment include attention and concentration, memory, visual-spatial skills and executive functioning (Michaud, Forget and Cohen 2009 Pereira, Tiemensma, Romijn and Biermasz 2012)

### EFFECTS OF CHRONIC CORTISOL SECRETION ON THE BRAIN: COGNITIVE SYMPTOMS

Several areas of the brain have high numbers of cortisol receptors.

- Hippocampus- necessary for memory formation
- Amygdala- responsible for our fear and anger response
- Frontal lobes- the executive director of the brain.

These brain areas, particularly the hippocampus, experience volume loss in patients with Cushing's syndrome thought to be due to excitotoxicity.

### THE GOOD NEWS

The structural changes in the brains of individuals with Cushing's syndrome were reversed following successful treatment. (Bourdeau et al 2005).

 However, reports of cognitive impairment in Cushing's syndrome also persist despite long term hormonal regulation (Pereira et al 2012), although this is not well studied.

## LONG-TERM COGNITIVE CHANGES IN CUSHING'S SYNDROME?

There may be overlap with persistent psychological symptoms, as some of the core symptoms of both depression and anxiety are cognitive dysfunction (e.g. difficulty concentrating, problems with new learning and memory, indecisiveness).

Very few studies looking at cognitive functioning in Cushing's syndrome control for the role of emotional functioning.

### STUDIES EXAMINING PERSISTENT COGNITIVE DEFICITS IN CUSHING'S

There have been only two controlled studies assessing cognitive functioning in patients with Cushing's using standard neuropsychological tests.

The first looked at cognitive changes in patients with Cushing's disease prior to treatment only, and did not assess the role of emotional functioning in cognition at all (Forget, et al 2000).

### RESULTS FROM TIEMENSMA ET AL, 2010

- The second compared neuropsychological performance in Cushing's patients in remission to controls. Controls were matched for age, gender, and education. Further, controls included both healthy individuals, and those with a history of and aged following treatment for nonfunctioning pituitary macroadenomas.
- Results indicated impairments in memory and executive functioning in the Cushing's group as compared to controls in the pituitary macroadenoma group.
- However, while a measure of depression was administered, these results were not reported, thus the role of depression affecting performance is unknown.

### CLINICAL FINDINGS FROM PATIENTS AT EMORY: PROTOCOL

- Cognitive Assessment including formal evaluation of
  - Effort
  - Attention and Concentration
  - Processing Speed
  - Language
  - Visual Spatial Skills
  - Learning and Memory for both verbal and visuospatial information
  - Executive Functioning
  - Intellectual Functioning

Emotional Assessment including

- Standard clinical interview assessing psychological symptoms
- Completion of detailed self-report measures assessing psychological functioning including
  - Depression
  - Anxiety
  - Anxiety-Related disorders (Panic, PTSD, OCD)
  - Mania
  - Somatization
  - Psychosis
  - Substance Abuse

### FINDINGS FROM CUSHING'S PATIENTS AT EMORY

Demographics:

- 16 patients with Cushing's syndrome were seen for a full neuropsychological evaluation in our clinic from 2014-2019
- Ages range from 22-59
- 12 females, 4 males
- Of the 16 seen, 4 patients had repeat evaluations. 2 patients had pre and post surgical testing, for the other 2 both assessments were after surgery.
- 9 had normal cortisol levels (biochemical remission), and 5 had elevated cortisol
- All patients passed symptoms validity measures indicating good effort on testing

### CUSHING'S PATIENTS AT EMORY: FINDINGS FROM PRE AND POST TESTING

- Patient 1 Pre Surgery:
  - Cognitive findings of decreased speed of processing (mild impairment), mild impairment with new learning for visuospatial information
  - Emotional findings of acute mania, which resulted in hospitalization prior to surgery. Also symptoms of depression and anxiety
- Post Surgery:
  - Cognitive Findings: Intact speed of processing, continued mild impairment with new learning for visuospatial information
  - Mania resolved. Increased symptoms of depression and anxiety, which were thought to be contributory to residual cognitive problems.

### CUSHING'S PATIENTS AT EMORY: FINDINGS FROM PRE AND POST TESTING

- Patient 1I Pre Surgery:
  - Cognitive findings of decreased speed of processing (mild impairment), moderate to severe impairment with new learning and memory for verbal information.
  - Emotional findings of anxiety.
- Post Surgery:
  - Cognitive Findings: Intact speed of processing, continued impairment with new learning and memory for verbal information, with improved recognition memory.
  - Severe depression and moderate anxiety, with higher levels reported than prior to surgery. This was thought to be contributory to residual cognitive problems.

### FINDINGS FROM CUSHING'S PATIENTS AT EMORY: PATIENTS WITH ACTIVE DISEASE (N=5)

**Emotional Findings:** 

- All patients had clinically significant symptoms of emotional distress
- Depression (5/5)
- Somatization (4/5)
- Anxiety (2/5)

### FINDINGS FROM CUSHING'S PATIENTS AT EMORY: PATIENTS WITH ACTIVE DISEASE (N=5)

**Cognitive Findings included:** 

- Mild deficits with sustained and complex attention (4/5)
- Decreased processing speed (2/5)
- Decreased learning for new information (1/5)
- Two patients had no objective evidence of cognitive impairment

### FINDINGS FROM CUSHING'S PATIENTS AT EMORY: PATIENTS IN REMISSION

- Of the patients in remission, 4 had additional radiation treatment. 3 of the 4 had objective cognitive deficits on testing. All 4 were endorsing symptoms of emotional distress (depression, anxiety, and somatization).
- 6 patients were tested in biochemical remission:
  - All 6 reported persistent cognitive problems
  - 4 of the 6 had no objective cognitive deficits on testing
  - 1 of the remaining 2 had deficits inconsistent with Cushing's disease (undiagnosed learning disability).
  - 5 of the 6 had clinically significant evidence of psychological impairment; based on standardized psychological measures; typically symptoms of depression or somatization.

### TREATMENT?

Studies are needed to see if residual psychological problems resolve with empirically supported treatments (typically a combination of psychotropic medication and psychotherapy).

In patients that report persistent cognitive difficulties, several steps should be taken to evaluate concerns.

### TREATMENT?

- A formal neuropsychological evaluation should be conducted that includes measures of performance validity and measures of emotional functioning.
- If actual cognitive impairments are noted, the patient may benefit from cognitive rehabilitation to teach compensatory strategies
- If cognitive impairments are not found, but the patient continues to have subjective symptoms, psychological factors are likely at play. Treatment with Cognitive Behavioral Therapy to reduce focus on perceived errors may be a good option.

### THANK YOU!

### **Questions?**

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