Glucocorticoid Withdrawal Syndrome

Richard J. Auchus, MD, PhD, FACE The James A. Shayman & Andrea S. Kevrick Professor of Translational Medicine Division of Metabolism, Endocrinology & Diabetes Departments of Internal Medicine & Pharmacology

Disclosures

Contracted Research

- Novartis Pharmaceuticals
- Neurocrine Biosciences
- Spruce Biosciences
- Corcept Therapeutics
- Diurnal, LTD

Consultant

- Quest Diagnostics
- Corcept Therapeutics
- Janssen Pharmaceuticals
- Novartis Pharmaceuticals
- Strongbridge Biopharma
- Crinetics Pharmaceuticals
- Adrenas Therapeutics
- PhaseBio Pharmaceuticals
- OMass Therapeutics
- Recordati Rare Diseases
- H Lundbeck A/S

Cushing Disease Case 1

- 37 YO WF, Wt Gain, High BP, Amenorrhea, Hirsutism
- +Poor Sleep, +Bruising, Difficulty Climbing Stairs
- PE: BP 158/97, +Facial Plethora, Moon Facies, +Bruises, +DC & SC Fat Pads, 1-1.5 cm Purple Striae, Reduced Proximal Muscle Strength, Moderate Facial Hair
- UFC 320 μg/24 h, ACTH 55 pg/mL
- MRI: 8 mm Pituitary Adenoma
- IPSS: 100x Gradient to Left IPS, 20x Gradient Right IPS

How Do You Counsel This Patient?

- We just need to send you to a good surgeon
- Lowering your cortisol will make everything better
- You will go back to exactly how you were before
- I have some good news and some bad news



Perioperative Cushing Disease Care Some Definitions

- Central Adrenal Insufficiency
 - -Inadequate Cortisol Production Via ACTH Deficiency
 - -Normally Transient After TSS For Cushing Disease
- Glucocorticoid Withdrawal Syndrome (GWS)
 - Symptoms After Rapid Lowering of Chronically Elevated Endogenous or Exogenous Glucocorticoids
- Adrenal Axis Recovery
 - Biochemical Normalization of ACTH and Cortisol After Glucocorticoid Tapering INDEPENDENT of Symptoms

Typical GWS Symptoms

- Constitutional
 - -Fatigue, Hypersomnolence, Asthenia
- Musculoskeletal
 - -Myalgias, Arthralgias, Persistent Weakness
- Gastrointestinal
 - -Anorexia, Nausea, Vomiting
- Neuropsychiatric
 - -Mood Swings, Depression, Anxiety
- Distinguish From Chronic Morbidities

Pathophysiology of GWS Symptoms

- Not Much Known, Though Well Recognized
- Elevated Cytokines IL-6, IL-1β, TNF-α
 - -Withdrawal of Immunosuppression
 - -Not Suppressed By Physiologic Dose Dexamethasone
- Repair of Damaged Tissue – Reversal of Cortisol Catabolic Activity
- CRH Suppressed

Withdrawal vs Al vs Recurrence



He et al Pituitary 2022;25:393

Cushing Disease Case 1 – Scenario 1

- Pituitary Surgery: Good Exposure & Resection
- POD 1-2-3 Cortisol 6-9-8 μg/dL
- Feels Better, BP Improving, Eating Well
- Discharged 20 + 10 mg Hydrocortisone
- Tapered Off Treatment in 6 Weeks
- UFC 40 μ g/24 h, AM Cortisol 10 μ g/dL, ACTH 25 pg/mL
- Exam: BP 140/85, Improved Plethora, 5 lb Weight Loss, Less Bruising, Same Facial Hair

How Do You Counsel This Patient Now?

- You are cured!
- I told you this would be a breeze
- You do not need any follow-up testing
- You are probably going to have a recurrence

Cushing Disease Case 1 – Scenario 2

- TSS: Good Exposure & Resection
- POD 1-2-3 Cortisol 2-<1-<1 μg/dL
- BP Improves, Appetite Fair
- Discharged 20 mg TID Hydrocortisone
- Called 1 Week Later
 - Unable to Stay Out of Bed >1 h
 - No Appetite, Nothing Tastes Good
 - Crying Spells, Withdrawn, Hurts All Over
- What Do You Tell Her Now?

Crash And Burn



What Do Patients Say?

Table 5. Patient concerns mentioned in the final open-ended question of the phase 2 patient survey

Patient concern (N = 280)	% (n)	95% CI	Sample quotations
Felt unprepared for recovery and/ or wanted more information on recovery Providers were not familiar enough with CS or provided inaccurate information	32.9 (92) 16.1 (45)	27.6-38.6 12.2-20.8	"[I needed] better aftercare." "I wish someone would have told me what I would be experiencing after surgery." "Information on how to recognize adrenal insufficiency/crisis would have been helpful." "I am 'in the dark' as to what's going on at this point." "Recovery from having Cushing's has been really rough for me and my family. We had no idea what to expect, or how
			 In the second problem of the second
			 "I am shocked that most medical professionals are NOT FAMILIAR with Cushing's syndrome or its recovery." "I just wish physicians were more familiar with Cushing's. It is so frustrating [and] adds to the mental exhaustion of trying to fight off this debilitating disease." "I wish my endocrinologist had prepared me for what to expect in recovery She said I would be able to return to work 2-3 weeks after surgery. It took me 3 months before I could return to work."

Acree et al J Endocr Soc 2021;5(8):bvab109

Before Surgery

- EDUCATE Patient About GWS
 - -Onset ~1 Week After Successful Surgery
 - Do NOT Sugar-Coat The Challenges To Come!!
- GWS is EXPECTED
- Having GWS Favors DURABLE REMISSION
- GWS is HIGHLY VARIABLE
- GWS WILL END SOMEDAY
- I Will Help You To Get Over GWS
- Family & Friend Support Critical

Managing GWS: Scylla & Charybdis



Early Postoperative Care To 12 Weeks

- Watch For Hyponatremia, CSF Leak, DVT/PE
- Over-Replace Initially, Small Steps Down
- Initiate Circadian Distribution ASAP
- Emphasize Evidence For Healing
 - -BP, Glucose Early
 - -Skin/Bruising Next
 - -Weight Loss, Fat Redistribution, Strength Later

Late Postoperative Care 3-12 Months

- Test & Taper
 - -Entrain Circadian Rhythm
 - -Forced Glucocorticoid Dose Reduction
 - -Test Other Axes & Replace
- Supportive Medications
 SSRIs or SNRIs, NSAIDs
- Supportive Measures
 - -Physical Therapy
 - -Cognitive/Behavioral Therapy

Postoperative Tapering & Testing



He et al Pituitary 2022;25:393

Long-Term Care/End Game

- Manage Hypopituitarism if Present
- Assess Cognitive and Physical Function
- Annual Screening For Recurrence

Chronic Cognitive Dysfunction

Resmini J Clin Endocrinol Metab 2012;97:663



Andela Eur J Endocrinol 2015;174:R1

Chronic Myopathy

Vogel Eur J Endocrinol 2021;184:813



Vogel J Clin Endocrinol Metab 2020;105:e4490

Cushing Disease Recovery is a Marathon

