Cushing's Support & Research Foundation
Winter/Spring 2019

cushing's newsletter

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Rare Disease Summit: A New Era of Patient Focused Innovation

Leslie Edwin and Amy Dahm

Two delegates – Leslie Edwin, President, and Amy Dahm, "DC Correspondent" – represented the CSRF at the National Organization for Rare Disorders (NORD) Orphan Products Breakthrough Summit at the Marriott Wardman Park in Washington, DC October 14-16, 2018. Sam, Amy's service dog, accompanied them to the conference and information sessions. The NORD Summit is one of the most important meetings of the year because it is the only platform that brings scientists, researchers, patient advocacy organizations, finance, pharma, government, regulators, and clinicians all under one roof. It's a great time to learn about best practices, legislation, and innovations that affect hundreds of thousands of people in the rare disease community.

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A message from our founder

This newsletter is especially meaningful to me. I have been in the process of winding down with CSRF for the past few years. It has been very difficult for me to let go of my role as President. I have literally put my heart and soul in this Foundation, but I realize it is now time to hand it over to Leslie and others that will carry on with my journey.

The CSRF has been the mainstay of my life for the past 24 years. As I reflect on my journey, and, it has indeed been a journey, I am focused on all I have been witness to and all that has been bestowed upon me. Yet, most life changing, most enduring, has been the gratitude that envelopes and protects me. I say protect, because without the gratitude, I am sure I would be heartbroken. But I am not heartbroken today. I am filled with gratitude for all I have enjoyed in helping people, and millions of moments of what makes my life meaningful.

My message today is one of thanks. Thank you to all who believe in our mission. Thank you all who help us achieve our goals…all the hours that our Directors have given, I will be forever grateful. To our amazing physicians on our Board who believe in us, I think the world of you all. And thank you, from the bottom of my heart to the thousands of patients who have shown me what truly matters.

With abiding gratitude,
Louise Pace

FOLLOW THE CSRF ON TWITTER!
We will be tweeting whenever new content is added to our website or there is breaking news. To follow us, sign up at:

https://twitter.com/CSRFnet

Do you have a QR Code Reader on your phone or tablet?

We are trying something new with this issue and would like your feedback on using these codes for quick access to links to more information. There are many free options in your device's app store if you're interested in checking it out.

CSRF Welcomes New Medical Advisory Board Members

DR. THEODORE H. SCHWARTZ

Dr. Theodore H. Schwartz is the David and Ursel Barnes Endowed Professor of Minimally Invasive Neurosurgery and a Professor of Neurosurgery, Otolaryngology and Neuroscience at Weill Cornell Medical College, New York Presbyterian Hospital. He is the Director of Surgical Neuro-Oncology, the Director of Anterior Skull Base and Pituitary Surgery, and runs a fellowship in surgical neuro-oncology. He specializes in the treatment of Brain, Skull Base and Pituitary Tumors using the latest techniques in minimally invasive endoscopy. Dr. Schwartz received his undergraduate and medical degrees from Harvard University where he graduated Magna Cum Laude. After completing his residency and chief residency in Neurosurgery at Columbia-Presbyterian Medical Center he then pursued advanced fellowship training at Yale-New Haven Medical Center.

Dr. Schwartz specializes in the treatment of pituitary tumors and Cushing's Disease. He has authored over 300 publications on the subject of pituitary surgery as well as 5 textbooks, including the first textbook dedicated to Endoscopic Pituitary Surgery (Thieme) and a textbook titled Transsphenoidal Surgery (Springer). Dr. Schwartz was awarded the Gentle Giant Award by the Pituitary Network Association in 2013 for his work caring for patients with pituitary tumors. He does approximately 100 pituitary surgeries per year and has performed over 1500 transsphenoidal surgeries.

DR. GEORGIANA ALINA DOBRI

"I have been captivated by the complex interactions of the pituitary hormones since I first came to learn about them, and I have made studying these disorders the focus of my work. I am committed to helping the patients whose lives are so deeply affected by them.

Cushing syndrome is probably the most challenging endocrine disorder to diagnose and treat; thinking outside the box and at times using dynamic hormonal testing are required to tackle it.

"It is a privilege to provide outstanding, compassionate endocrine care for patients with pituitary and adrenal pathologies or neuroendocrine tumors. I take a multidisciplinary approach to these disorders and work very closely with my colleagues in neurological surgery, endocrine surgery, ENT, neuroradiology, neuro-ophthalmology, and neuropathology at the Weill Cornell Pituitary Clinic to ensure comprehensive and expedient evaluation and treatment."

DR. NICHOLAS TRITOS

Dr. Tritos serves as Associate Professor of Medicine, Harvard Medical School and staff neuroendocrinologist, Neuroendocrine Unit, Massachusetts General Hospital in Boston. His clinical and research interests include pituitary tumors, growth hormone deficiency in adults and regulation of energy homeostasis. He has served on several professional society committees, has authored over 105 peer-reviewed publications and 20 book chapters and serves as editorial board member for several professional journals.

Prescription Assistance

There are many prescription drug cards that can be found by searching the internet. The CSRF does not endorse any specific card. One that has recently come to our attention is **UNA Rx** card which can be used nationwide. More information is available at *http://www.unarxcard.com/index.php*

Rx Hope is another program with discounted prescription pricing: *https://www.rxhope.com/*

PAN has programs for some of the medications specific to Cushing's including Korlym and Signifor: *https://www.panfoundation.org/*

NORD also provides help with medication costs as well as travel and other medical expenses: *http://rarediseases.org/for-patients-and-families/help-access-medications/patient-assistance-programs/*

Call: 1-800-999-6673 x 326
Email: Cushings@rarediseases.org

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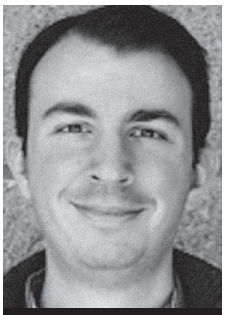
NORD MEMBERS PRE-CONFERENCE MEETING

The day before the official launch of the conference, we attended the NORD members-only Pre-Conference Meeting. NORD representatives staffed themed networking tables, and delegates discussed topics such as Patient Assistance Programs in depth. One of the highlights was a panel featuring case studies of different organizations' social media fundraising strategies using FaceBook, Twitter and YouTube. Panelist Vanessa Vogel-Farley, Executive Director of rare disease patient group Dup15q Alliance, emphasized the importance of building a strong donor community by utilizing social technology. Small rare disease groups have common challenges when it comes to fundraising, and these pre-conference meetings are excellent opportunities to network and see what others are doing to fund their efforts to improve outcomes for patients.

Gabriel Low

Taylor Kane

Harjot Randhawa



Chris Anselmo

Relatedly, another panel, "Collaboration with Industry: Partnerships, Potential, and Pitfalls," examined the benefits and challenges of patient organizations partnering with industry. This topic frequently finds itself in critics' crosshairs, but the scrutiny is an opportunity to achieve greater transparency. Partnerships with companies who make specialty drugs for tiny populations such as ours can be mutually beneficial. There are thousands of rare diseases that have zero drugs created solely to treat their condition, and manufacturers of generic medications and those that are used off-label do not seem to make the same investment in educating and supporting their rare communities.

MAIN CONFERENCE OPENING REMARKS AND YOUNG ADVOCATES

Peter Saltonstall, President and CEO of NORD, opened the conference with a brief welcome and summit preview. The theme for 2018 was "A New Era of Patient-Focused Innovation". There does indeed seem to be a ramping up of interest in patient-focused outcomes and the patient voice influencing research, so we were excited to see NORD's focus on the topic. This welcome implored all stakeholder attendees to invest in the human relationship in medicine and to take time to get to know patients.

Every year immediately following Mr. Saltonstall's opening address there is a Young Advocate panel that showcases the next generation of patient advocacy and discusses ways patients are assuming innovative roles to help advance research. Four young adults – Gabriel Low, Taylor Kane, Harjot Randhawa, and Christopher Anselmo – shared their personal stories of how they became involved in rare disease advocacy. Scan the QR code to learn more about each (web addresses for more information about these three are included in the footnotes of this article if you do not use a QR reader). Dr. Anita Gupta, a physician and rare disease survivor, moderated the panel and stated that "somewhere in all the education, we sometimes forget empathy and compassion. Sometimes it's becoming a patient that makes us appreciate the experience of a patient."

HOW PATIENTS ARE HELPING DRIVE RESEARCH AND DRUG DEVELOPMENT

There are many ways that patient input and involvement in research will improve outcomes for current and future patients. Simply lending your voice to a survey or questionnaire could have an enormous impact - the information is used by researchers who ultimately publish the studies that are used by clinicians to, for example, figure out what to do when they encounter the first Cushing's patient of their career.

Patients bring focus, relevance, and urgency to the research process. Scientists are curious, but when working with patents they can be more likely to adhere to the single problem they are addressing in the trial; they may not be aware of other problems to address. To get a seat at the table, we have to establish the fact that we are the authorities on our disease. We need to attend meetings and reach out. It is vital to make sure at all times that clinicians, researchers, and pharma are clear on what we, the patient population, actually consider the most important outcomes. Collaboration is essential to everyone's ability to work at maximum effectiveness.

There are about 250 new rare diseases defined every year, and there are currently about 7000 known rare diseases. There is no sign that these numbers will decrease; genetic research is increasing this number more than anything. These large numbers can be daunting when

NORD young advocates panel

taken as a whole, so it is recommended to "act locally, think globally". Many good ideas for single patient communities can be adapted for others.

SOLVING THE DIAGNOSIS CHALLENGE

Shortening delays in diagnosis is a huge challenge facing not only Cushing's patients but the rare disease community as a whole. Big opportunities for genetic research, especially over the last decade, have come from efforts to address unmet needs and other delays in diagnosing a rare disease. The National Institutes of Health (NIH) has an Undiagnosed Diseases Program (UDP), which is part of a larger national network aimed at finding and diagnosing patients who have been passed around multiple specialists with no conclusive testing or discovery. The NIH reports that the majority of successful diagnoses through this program are the result of physicians coming together to discuss cases and crowdsource their wisdom and experience, not from testing alone. You can learn more about the UDP by scanning the QR code or visiting *https://www.genome.gov/27543155/udp-background/.*

USING TECHNOLOGY AND ARTIFICIAL INTELLIGENCE (AI): THERE'S AN APP FOR THAT

One of the most fascinating sessions explored how to use technology and AI to assist doctors in diagnosing and identifying rare disease and to help patients shorten their diagnostic timeframe. Dr. Christine Stanley, Head of the US Clinical Laboratory for WuXiNextCode, presented on how to integrate phenotype to diagnose more patients *(yourdictionary.com explains the difference between genotype and phenotype well – **genotype** is the set of genes in our DNA which is responsible for a particular trait, while **phenotype** is the physical expression, or characteristics, of that trait).* Dr. Marius Lingararu from Children's National Health System discussed the development of an app that can scan the features of a newborn's face and determine whether the infant is at low, medium, or high risk of having a particular disease. This early detection of dysmorphology (birth defects) helps to accelerate diagnosis so patients have access to treatment at the earliest possible opportunity.

Oodaye Shukla, Chief Data Scientist at analytics company HVH Precision, discussed an emerging technology that allows its scientists to analyze large data sets to find patient pools that have symptoms consistent with that disease to ultimately lead to quicker diagnoses, especially for rare diseases. HVH is looking to partner with Cushing's patients who could help inform and guide a patient-based collaboration. If you are interested, please scan the QR code or visit HVH's website at *https://www.hvhprecision.com for more information about the company, then contact Amy Dahm at a_dahm@yahoo.com.*

FOOD AND DRUG ADMINISTRATION (FDA) COMMISSIONER KEYNOTE

Dr. Scott Gottlieb, FDA Commissioner (has since resigned the position), was scheduled to give the keynote address but was called away the morning of the meeting for an emergency elsewhere in DC. Dr. Rachel Sherman, Principal Deputy Commissioner of the FDA, stepped in and delivered the keynote on the topic of "NORD Membership: Integrity, Responsibility, Strength."

Dr. Sherman talked about another topic that is getting a lot of attention right now – patient registries. These databases of patient-report-

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NORD leader member group

Amy Dahm and her service dog Sam.

ed information are extremely important and as such are one of very few areas in which the FDA gives grants. If you want a few excellent examples of the type of research that can be pulled from registries, please scan the QR code or search PubMed (https://www.ncbi.nlm.nih.gov/pubmed) for Dr. Elena Valassi's work using the European Register on Cushing's Syndrome – (ERCUSYN).

The mission of the FDA is to get products to patients, and they are constantly expanding ways for patients to connect and participate in the process. To challenge the idea that patient participation in FDA processes or genetic testing is out of reach for most, she pointed out that over 15 million consumers have purchased DNA kits from online retailers like 23andMe and Ancestry. If it was possible for actual genetic counselors to access this information, who knows what significant breakthroughs could be achieved. It might be a bit of oversimplification, but the point is correct that patient participation in genetic mapping could be "just as easy".

THE PATIENT FAIR

Every year there is an open fair showcasing resources, drugs, and organizations that assist patients. One of the organizations, Patient Airlift Services (PALS), based in Farmingdale, NY, offers free air transportation to patients needing specialized treatment or follow-up at a distant facility, patients who have a large number of visits, and those in fragile health who must avoid public places because of compromised immune systems. PALS' number is 631-694-7257 and website is *http://www.palservices.org/, or scan the code.*

FEDERAL POLICY PRIORITIES AND RARE DISEASE LEGISLATION

Unfortunately, the picture is not very clear right now out of Washington. NORD's position is that the issue of drug costs is so massive that not much is likely to change any time soon. Matters of adequate and affordable insurance aren't going anywhere, either. Data suggests that the significant rate increases seen in 2018 were "too high and based on actuarial-predicted inflated costs that did not end up happening". Since another major election looms now, it is likely that a lot of chatter will swell on this topic because it is a hot button for candidates to discuss their stances.

It is confusing to try to decipher biased summaries about legislation up for discussion and vote; a good example of this would be the Right to Try law (Senate Bill 204) that was signed into law in May 2018. This law allows patients to access investigational drugs outside of clinical trials if there are no other treatments available and they can't participate in a trial. Usually these patients are extremely sick. NORD was very vocally opposed to this bill, which might sound odd at first considering they advocate for rare patient access to medications. The opposition came from a stance, supported almost unanimously by member organizations, that an already vulnerable group of people (very sick, rare) would become more exposed to dishonest dealings. The FDA already approves 99.5% of applications for emergency drug needs through their Expanded Access program, sometimes on the same day they receive the application. So technically, they already have something in place for fast-tracking medicine to those in dire need of it.

Peter Saltonstall

If you are interested in participating in the legislative process, you do not need a lot of experience or special contacts to get involved with your state and district delegations. Even a single conversation can lead to building bipartisan support for rare disease issues. NORD's Rare Access Networks now operate in all states, are volunteer-led, and are always looking for passionate individuals to help participate in, organize, and present rare issues locally. If this interests you, please scan the QR code or visit *http://rareaction.org/get-involved/join-rare-action/ for more information.*

To read more about the young advocates mentioned at the beginning of this article, please check the websites listed below.

Gabriel Low: *https://katu.com/news/local/teen-stops-in-portland-during-cross-country-bike-ride-raising-awareness-of-rare-diseases*

Taylor Kane: *https://sjmagazine.net/women/girl-power-profile-taylor-kane*

Harjot Randhawa: *https://rarediseases.org/early-diagnosis-perspectives-from-nord-student-chapter-leader-harjot-randhawa/*

Christopher Anselmo: *https://www.statnews.com/2016/02/29/rare-disease-dysferlinopathy/*

If You Shop at Amazon....

If you shop at Amazon.com, consider shopping through Amazon Smile, which lets you donate .5% of your purchase to your charity of choice. The link to shop at Amazon and support the CSRF is:
http://smile.amazon.com/ch/04-3271267

amazon.com

Want to be on the CSRF mailing list?

If you aren't already on our mailing list, you can join through our web site at www.CSRF.net — Member Services, or just return this form to: CSRF, 4155 Lawrenceville Highway #8130 Lilburn GA 30047. **All memberships are free.**

Name

Address

City *State* *Zip*

Phone

Email

Suggested donation is $30.00 or whatever is best for you. All donations are tax deductible. Please make checks payable to CSRF. Memberships without associated donations will be automatically converted to electronic newsletters in 2019. An annual donation in any amount will trigger a 3-issue print subscription.

Are you a Cushing's patient?
☐ YES ☐ NO

Did you have:
☐ pituitary tumor ☐ adrenal tumor ☐ other

Would you like to discuss publishing your story in a future issue of the newsletter?
☐ YES ☐ NO

What would you like to see addressed in future issues?

Doctors' Answers

Q My daughter has just been diagnosed with cyclic cushing's… I have done some reading and found this article: *https://academic.oup.com/jcem/article/97/10/E1836/2833262*. Is hair testing done in the US?

ANSWER 1:

I'm not aware of any commercial laboratory that offers hair cortisol testing in the U.S. However, it is not clear why this is needed if someone has made the diagnosis and it is clear-cut. There are some things to keep in mind, however, even if the diagnosis is clear. Our testing for the cause of Cushing's syndrome presumes that cortisol levels are high enough for sufficient time to cause the normal pituitary cells to stop secreting ACTH, the hormone that stimulates the adrenal glands to make cortisol. We call this a feedback system that helps to keep cortisol in the correct range. In patients with cyclic Cushing's syndrome, it is possible that the cortisol levels are not high enough or don't stay high long enough to stop ACTH from the normal cells. In that case, when we measure ACTH to help determine the cause of Cushing's, it is possible that we will measure ACTH from the normal cells and get a misleading result. For this reason, my group asks patients, especially those with possible cyclic Cushing's syndrome, to measure a 24-hour urine for cortisol, and obtain a salivary cortisol at bedtime on that day. We do this once a week for six weeks, and if the numbers are high, we admit to evaluate for the cause of Cushing's syndrome. (Dr. Lynnette Nieman, NIH)

ANSWER 2:

I'm not aware of a lab in the US performing this for patient care. It is an interesting concept that is worth researching more and might be a useful diagnostic tool for the future. The patients included in this study have fairly high 24h urine cortisol levels and it would be interesting to see more patients with milder Cushing and pseudo-Cushing (endogenous elevated cortisol not related to a tumor) to tease out a cutoff/normal range that would be helpful in early diagnosis. (Dr. Georgiana Dobri, Cornell)

ANSWER 3:

Hair cortisol is not available for routine use in the clinic at present. However, it is being used in research studies in several countries. Although it appears promising, its value as a test in patients with suspected (cyclic) Cushing's remains to be proven. It is not clear, for example, if hair dyes, shampoos and exposure to the elements (sun, water) can affect hair cortisol levels. More research is needed before this test can be recommended to our patients. (Dr. Nicholas Tritos, Massachusetts General Hospital)

Q We found a small tumor on my pituitary when performing an MRI because of another issue. My doctor did some cortisol testing but most of my levels are normal and I don't have symptoms of Cushing's. I found a lot of information online about harmless adrenal tumors and why a patient should have periodic testing to make sure they aren't starting to cause problems, but I didn't find anything similar about pituitary tumors. Should I worry about this?

ANSWER 1:

I would not worry about it, but would consider getting a repeat MRI of the pituitary gland at some interval to be sure that the tumor is not increasing in size. Your endocrinologist can help decide when this is done, based on the current size of the mass. In general, we worry about two things with pituitary tumors: whether they are functional (i.e. making hormones) and whether they are big enough to hurt nearby structures. Unlike the adrenal gland tumors, non-functioning pituitary tumors almost always remain non-functioning. In your case, if excess prolactin, growth hormone, alpha subunit, LH, and FSH have been excluded in addition to the normal Cushing's workup, it's very unlikely that the tumor will become hormonally active. On the other hand, the size is important. About 10% of healthy people have a non-functioning pituitary mass up to about 6mm in diameter. These rarely enlarge. However, many physicians would re-check to be sure that a smaller mass is not growing, and if the mass is larger than 6mm, and definitely if it is more than 10 mm, repeat imaging is done to be sure that there is no growth. (Dr. Lynnette Nieman, NIH)

ANSWER 2:

The finding of an incidental small pituitary tumor (pituitary "incidentaloma") on MRI is not rare. Well-defined studies have shown the presence of small pituitary tumors at autopsy in 22.4% of randomly selected cases (Toronto) and 3% of randomly done MRI scans (Amsterdam). At USC, we followed a group of 27 patients with microadenomas for 10 years during which time three of the tumors grew significantly. Interestingly, all three were 6mm or greater in size when first discovered, and growth was observed within four years of initial discovery. Although the vast majority of microadenomas do not grow, obviously some do or we would not see macroadenomas. Therefore, a patient with an incidentally found non-functional microadenoma should be followed by repeat scanning. Our protocol is to follow pa-

tients with MRI scans annually for five years. If no growth in that period, we get another scan at seven years and one final scan at 10 years. If no growth by 10 years, we do not get additional scans. The 10 year scan may be somewhat excessive, but we tend to err on the conservative side in that respect. (Dr. Martin Weiss, University of Southern California)

ANSWER 3:

Adenomas do not change in characteristics, in other words if they are non-functioning they remain non-functioning. Conversely, some adrenal tumors can produce more cortisol with time. If your doctor has completely ruled out Cushing's with at least two different kinds of tests (two 24 hour urine, bedtime saliva, and dexamethasone suppression test) there is no need to repeat the Cushing work up. (Dr. Roberto Salvatori, Johns Hopkins Pituitary Center)

ANSWER 4:

The words I'm picking up here – "some cortisol testing and most levels are normal" – would make me recommend a full workup either now or in some months from now to further look into mild Cushing that would declare with time vs nothing to worry about (2-3 midnight salivary cortisol, 24h urine cortisol, low dose Dexamethasone test with Dex level).

Up to 10-15% of the adrenal adenomas can start secreting cortisol later on and this is not generally the case with nonfunctional pituitary tumors if appropriately labeled so. On the other hand, I had a patient with normal IGF1 for years and known pituitary tumors who started to have progressive elevation in IGF1 and later confirmed to have GH producing tumor after surgery… so I now add an IGF1 along with the MRI for monitoring. (Dr. Georgiana Dobri, Cornell)

Q How is it possible for someone to have extremely high cortisol levels and not be obese or get stretch marks?

ANSWER 1:

Cortisol needs to be high for a long time to cause physical signs of Cushing's syndrome. Also, patients with similar cortisol values, for a similar length of time, often look different. We assume that this may reflect specific aspects of their type of Cushing's syndrome, but it is very likely that differences in our genes (the blueprint in our cells that codes for our physical appearance) make some people more likely to get certain features. (Dr. Lynnette Nieman, NIH)

ANSWER 2:

Elevated cortisol levels are common in many clinical situations that have nothing to do with Cushing syndrome and may or may not cause any signs or symptoms of excessive cortisol production: for example, birth control pills and pregnancy cause elevations of cortisol due to increases in the protein that binds cortisol in the blood. Elevations of urine cortisol also may occur in these women. Patients with eating disorders who may be very thin often have elevated cortisol levels. An increase in cortisol secretion is a well known adaptive response to starvation. Reddish or what we call violaceous stretch marks are a reflection of rapid weight gain in young people with or without Cushing syndrome and are unusual in patients over 40 years of age with Cushing's. On the other hand, patients with alcohol abuse may have very high cortisol levels which may cause some of the well known clinical manifestations of Cushing syndrome. Rarely, there are individuals who have resistance to cortisol and have elevated cortisol levels but no evidence of Cushing syndrome. (Dr James Findling, Medical College of Wisconsin)

Q I have had persistent Cushing's since 2012. I've had a couple of surgeries, radiation, and about 18 months of medical therapy. I came off that when the radiation seemed to be working – I was losing weight, my hair was growing back, and I could sleep. I'm currently just shy of three years post radiation. I've had "low cortisol" feelings enough that I take a small dose of hydrocortisone on most days (5mg in the morning probably 4 times a week) but a recent salivary cortisol test came back at double the normal limit. My doctor asked me to stop taking the HC but some days I feel like complete garbage and take one anyway. Without the ability to test my cortisol constantly, I feel like the occasional test is not an accurate picture of what the cortisol in my body is actually doing. Neither continuing the daily HC nor completely stopping it feels like the right decision. I continue to lose weight and have no problems sleeping or other Cushing's symptoms. Do you have any advice for managing this "gray area?"

ANSWER 1:

One concern is that the cumulative effect of all the treatments has also destroyed the normal pituitary cells that make ACTH, and that you may be slightly adrenally insufficient. It's important to recognize that radiation therapy does not restore the normal rhythm of ACTH production (and hence cortisol rhythms). Normally, if people have relatively routine sleep-waking habits, the ACTH and cortisol reach a low point just after falling asleep, and begin to increase before waking, so that morning values are much higher than bedtime values. By contrast, radiation reduces the level in the blood at all times of the day. In the most extreme case, when there is no difference in morning (waking) and nighttime (sleeping) ACTH/cortisol during Cushing's syndrome, the change after radiation is that the numbers remain similar but decrease. For this reason, a late night/bedtime salivary cortisol value will be similar to a morning value, and will be considered "abnormal" for nighttime. If the question is whether the Cushing's syndrome is not entirely in remission, it is better to get a 24-hour urine cortisol or to perform a 1 mg dexamethasone suppression test, which are not affected by the radiation. If your "elevated" evening salivary cortisol level was at the low end of the morning normal range,

continued

then it's possible that you do need cortisol. An ACTH stimulation test can help identify this problem. Remember too, that low cortisol levels are associated with weight loss, decreased appetite, fatigue and joint aches, which may be other clues as to your situation. (Dr. Lynnette Nieman, NIH)

ANSWER 2:
Was the cortisol test (salivary cortisol) done while you were taking hydrocortisone? If so, the test could be falsely high. In that case, it would be prudent for you to repeat the salivary cortisol test after avoiding taking hydrocortisone for at least 24 hours. It is certainly possible that radiation therapy can make the pituitary underactive over time, which can also make the adrenal glands underactive. Your doctor can measure your cortisol levels in the blood (for example, with a cosyntropin stimulation test) and determine if you need to take hydrocortisone every day. (Dr. Nicholas Tritos, Massachusetts General Hospital)

Q I have lost over 100 lbs since the worst of my Cushing's. I have a lot of loose skin including some on my neck and a fat roll in the middle that affects how my clothes fit. I've heard that patients in my situation can sometimes qualify for plastic surgery for medical purposes. Have any of your patients discussed this surgery with you?

ANSWER 1:
I have seen patients who had cosmetic surgery to remove the skin excess after dramatic weight loss with Cushing disease in remission or after gastric bypass surgery. I would suggest you consult a plastic surgeon who would send the appropriate paperwork to the insurance. If the endocrinologist needs to write a letter of support I'm sure it would not be an issue. (Dr. Georgiana Dobri, Cornell)

ANSWER 2:
Plastic surgery can be done to help improve the situation. It is often viewed as "cosmetic" by insurance companies that may decline to cover the cost of the procedure. However, the plastic surgeon may be able to convince the insurance to cover the cost, if they indicate that the procedure is medically necessary. For example, some people may experience discomfort or even skin infections in loose skin folds and can be helped by surgery to trim off the excess skin. (Dr. Nicholas Tritos, Massachusetts General Hospital)

Q I have confirmed hypercortisolism (enough highs after several months of testing) but no clear target. I'm morbidly obese, have lost my period, have new hair growth on my face, and almost all of the other classic Cushing's symptoms. If I have a bilateral adrenalectomy and just remove the source of cortisol production, will these symptoms go away? I'm willing to have adrenal insufficiency if it means these other things stop.

ANSWER 1:
They probably would, but BLA should be reserved for cases in which no other option is available. You need a diagnosis (do you really have Cushing, and if so, what is the cause? Is it ACTH dependent or independent?). Therapy will be then targeted to the underlying problem – pituitary adenoma, adrenal tumor, etc. (Dr. Roberto Salvatori, Johns Hopkins Pituitary Center)

ANSWER 2:
If ACTH dependent hypercortisolism is confirmed and nothing is on the brain MRI, an IPSS can help locate a minuscule pituitary adenoma or if the source is outside of the pituitary (ectopic). If ectopic source is confirmed you could have an octreoscan or even better a dotatate scan to try and find it and remove it. I would first try to find the culprit tumor before taking out the adrenals. If all the body changes are related to the excess of cortisol you should have significant improvement but it is important to have an in-depth discussion with your doctor so you have realistic expectations regarding the recovery. (Dr. Georgiana Dobri, Cornell)

ANSWER 3:
It is very important to answer this question in detail. Due to many false positives encountered in hypercortisolemia testing, Cushing's should be clearly confirmed – by elevation of cortisol (24 UFC and late night salivary cortisol), non-suppressibility to dexamethasone, and careful localization work-up. If complicated, testing preferably to be done in a tertiary Center.

No treatment should be started without clear diagnosis of Cushing's and establishing exact etiology, as there are many risks associated with each type of treatment. Recovery post-treatment depends on many factors, including severity and duration of the disease, but typically symptoms and features related to hypercortisolemia will slowly improve with time. (Dr. Maria Fleseriu, Oregon Health and Science University)

ANSWER 4:
This is a very important issue, especially with the Internet. We are a referral center for pituitary disorders and Cushing's patients, so I see a real spectrum – patients who have Cushing's and patients who suspect it is the cause of their weight issues, diabetes, depression, etc.

I explain that all of our screening tests are equally reliable: approximately 92% reliable [late night salivary cortisol, 24 hour urine free cortisol and 1 mg dexamethasone test]. I offer to re-test patients with multiple tests.

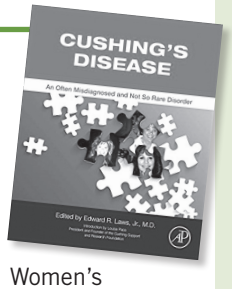
Because of the overlap of signs and symptoms with simple obesity and polycystic ovary syndrome, it may be difficult to assess these women clinically, so one thing I've learned over the years (and from the late Dr. Edward Oldfield) – sometimes "time" is the best test – so

if there is a question and variable test results, I will see the patient again in 4-6 months. (Dr. Mary Lee Vance, University of Virginia)

ANSWER 5:
Bilateral adrenalectomy is usually the last resort when other therapies have failed. Unfortunately despite progress in surgical and radiotherapy techniques several patients remain with active CD. Fortunately novel medical therapies now provide interesting options to control disease, but most of them are imperfect to restore completely normal HPA axis physiology or have side effects with impact on quality of life. Some issues result from financial costs with some medical therapies particularly when young patients consider chronic therapy over decades. Some young woman with residual CD desire fertility and cannot combine this with most medical therapies when cabergoline is not effective. So there are still some indications for bilateral adrenalectomy, but this has to be evaluated carefully in a multidisciplinary team approach with a well-informed patient in referral center with wide experience in CD and capacity for long term follow-up of permanent adrenal insufficiency, teaching in its care and continued follow-up of residual corticotroph tumor and co-morbidities. (Dr. André Lacroix, Université de Montréal)

Editor's Note: *Dr. Lacroix included a research article entitled "Bilateral Adrenalectomy in the 21st Century: When to Use it for Hypercortisolism?" with his answer; you can view it in its entirety by scanning the QR code on the Research Summary in this issue or visiting https://erc.bioscientifica.com/view/journals/erc/23/2/R131.xml.*

Cushing's Disease: An Often Misdiagnosed and Not So Rare Disorder



Edited by E. Laws, Jr., M.D., F.A.C.S., Professor of Neurosurgery, Harvard Medical School, Director – Neuro-Endocrine / Pituitary Program, Brigham and Women's Hospital, Boston, with an introduction by Louise Pace, Founder and President of the Cushing's Support and Research Foundation.

This comprehensive guide to Cushing's disease describes the functions of pituitary, adrenal and other hormones, lists the typical and atypical symptoms of Cushing's disease and its subtypes, outlines the causes of elevated cortisol and explains how clinicians can test for, diagnose and treat Cushing's disease. Physicians will find this concise book detailed, thorough and well-referenced. Patients will also find clear and helpful information in this important book. *Published in 2017 by Elsevier Inc – an excellent resource for physicians (and patients)!*

Need to talk? Local support groups and contacts

Many of you have expressed interest in local support groups and contacts. If you don't live in one of the following areas, consider starting a group in your area! Email the CSRF if you are interested. In particular, we have an existing group in the Los Angeles / Orange County area without an organizer.

San Francisco Bay Area, CA
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Research Article

Support Needs of Patients with Cushing's Disease and Cushing's Syndrome: Results of a Survey Conducted in Germany and the USA

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On September 3, 2018, Dr. Ilonka Kreitschmann-Andermahr of the University of Duisburg-Essen and her team received news that the manuscript for their first-of-its-kind, patient-reported quality of life research had been accepted for publication in the International Journal of Endocrinology. The CSRF was happy to participate in this research, with former Director Karen Campbell contributing valuable effort in the initial stages to the design and language of the questionnaire used.

We are happy to see more research being done into the quality of life needs of patients experiencing Cushing's, especially when patients' direct input is a large part of the data being collected and analyzed. We look forward to participating in and reporting on much more of this type of research in the future! In fact, Dr. Kreitschmann-Andermahr was conducting a follow up study at the time of publication of this issue; you probably got an e-mail invitation to participate. Once the results of that are made available we will share them with membership.

INTRODUCTION

Cushing´s disease (CD) and Cushing´s syndrome (CS) are illnesses characterized by symptoms due to prolonged exposure to elevated cortisol levels, which are associated with increased morbidity and mortality from metabolic, musculo-sceletal, infectious, thrombotic, cardiovascular and neuropsychiatric complications [1, 2]. In CD, the cause of the hormone excess is an adrenocorticotrophic hormone (ACTH) secreting pituitary adenoma, which stimulates adrenal cortisol secretion [1]. In CS, the reason for hypercortisolism may be exogenous (i.e. prolonged glucocorticoid treatment) or endogenous, such as a benign or malignant cortisol-secreting tumor of the adrenal gland or paraneoplastic ACTH secretion [3, 4]. With an incidence of 2-3/ million, CS and CD are rare diseases [5-7].

Clinical signs and symptoms of Cushing's include rapid weight gain, plethora, easy bruising, edema, proximal limb muscle fatigue, impaired glucose tolerance, mood disorders, such as depression and anxiety, cognitive difficulties, osteoporosis and cardiovascular problems [1, 4, 8-10]. First line therapy is the surgical removal of the hormone-secreting tumor and, in cases of iatrogenic CS, lowering the dose of or discontinuing glucocorticoids if possible. If hypercortisolism cannot be normalized by these measures, radiotherapy, steroid-lowering medications or bilateral adrenalectomy may also be employed in patients with endogenous CS and CD [11, 12]. However, next to other therapeutic side effects, treatment of CS and CD often leads to hypocortisolism necessitating hydrocortisone replacement therapy and bearing the potential complication of life-threatening Addisonian crisis [13].

On the basis of the above, it becomes immediately clear that CS and CD are chronic diseases that may not be easily cured and have long-term effects on patients' health, appearance, well-being and quality of life (QoL). Studies on patients with Cushing's confirm that patients' QoL can be impaired years after successful treatment even though the disease itself may be well-controlled or in long-term remission [9, 14-16].

In recent years, restoration of QoL in patients with chronic diseases has become an increasingly important treatment goal in clinical practice, resulting in the implementation of special support programs for many chronic diseases ranging from cancer and multiple sclerosis to diabetes mellitus [17-19]. It was, therefore, the aim of the present study to explore the disease burden and unmet support needs of patients with Cushing's against the background of developing strategies for targeted patient support beyond medical interventions.

PATIENTS AND METHODS

Patients: This cross-sectional patient-reported survey was conducted among adult (age ≥ 18 years) patients with CD who had undergone pituitary surgery for biochemically proven CD in two German neurosurgical university centers (Erlangen-Nuremberg and Duisburg-Essen) and patients with CD or CS who are members of the U.S. based Cushing's Support and Research Foundation (CSRF) and who also had already received diagnosis and treatment of CD/CS. Inability to fill in the survey was the only exclusion criterion.

Survey/Questionnaire description: A patient-reported outcome survey (PRO-survey) was developed to assess information about: 1) current burden of Cushing-related symptoms, 2) time points when support was needed the most, 3) factors that have helped the patients the most in coping with the disease, 4) disease-specific support needs, interest in a support program and topics of interest. These questions were compiled based on the results of former research by our group [10] and the current state of research on QoL and coping in patients with CD and CS [9, 14-16]. A neurologist (IKA), a neurosurgeon (MB), a psychologist (SoS) and, for the U.S. version of the questionnaire, one of the former directors (KC) of the CSRF developed the survey.

The survey comprised 14 questions to be answered based on given response options or as a free-text. The interest of the participants in a support program was assessed using a 5-point Likert scale, using the statements: not at all, a little, moderate, a lot and absolutely. The statements were coded from 1 (not at all) to 5 (absolutely) for statistical analyses. The questionnaire was developed in German, and for the U.S. participants was translated into English by a state-certified translator (IKA) and by native English speaking neurosurgeon in training (VK) and checked by KC to ensure comprehension of the translated questions.

For easier handling, the questionnaire was then programmed as an online-based survey that could be filled in by the U.S. patients via an activation link for a homepage sent by e-mail via the CSRF. The homepage was operated by the University Hospital Essen (Germany) and was hosted on a secure server of the hospital. The German patients received the paper-based version by mail.

The study was conducted in accordance with the Guideline for Good Clinical Practice and the Declaration of Helsinki [20, 21]. All patients gave informed consent and the study was approved by the Ethics Committee of the University of Duisburg-Essen.

Results: 84 U.S. and 71 German patients answered the questionnaire. There was no difference between groups with regard to sex and age ($p>0.05$, Table 1).

Disease burden: In response to the question "Which aspects of your Cushing´s condition bother/bothered you the most?" which assessed current or past disease burden, patients reported a variety of aspects which could be clustered into four major symptom groups (answers provided in a free-text field): 1) Symptoms related to cortisol overproduction (overweight, moon face, skin problems, sweating, muscle

continued

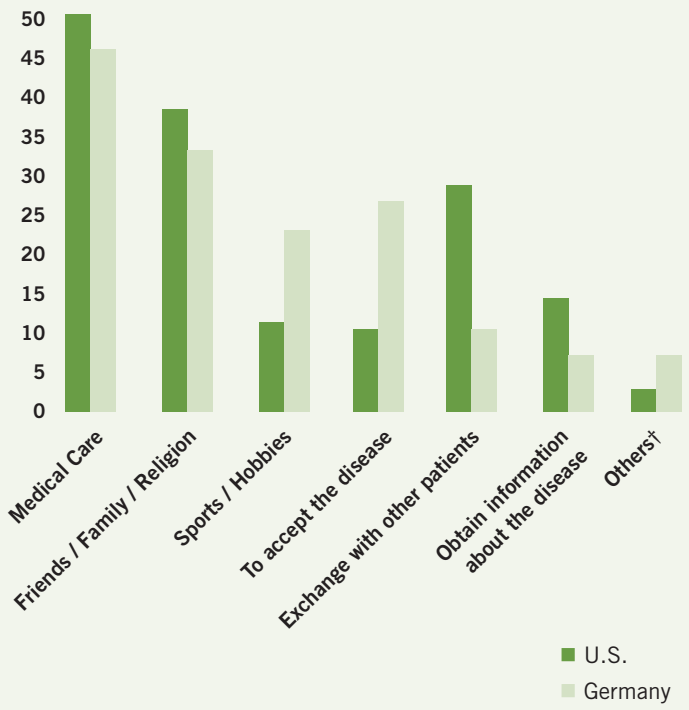
Table 1: *Characteristics of the study population for both groups. Data are presented as frequency (n) and valid percent (%) or mean ± standard deviation.*

Variable	US (n = 84)	Germany (n = 71)	p-Value
Sex			
Female	77 (91.7)	59 (83.1)	0.141
Male	7 (8.3)	12 (16.9)	
Age (years)	50.1 ± 13.73	48.8 ± 13.64	0.555
Reason for hypercortisolism			
Pituitary adenoma	56 (66.7)	71 (100.0)	
Adrenal tumor	21(25.0)	–	
Others†	7 (8.3)	–	

[a]*Fisher´s exact test.*

†Other reasons are: Pursuing ectopic or pituitary (n=1), bilateral macronodular adrenal hyperplasia (n=1), ectopic ACTH syndrome (n=2), steroid treatment (n=3).

Figure 1: *Factors that helped the patients the most in coping with the illness. Answers were provided in a free-text field and were clustered and counted. †Others are: nothing helped, time off work.*



weakness), 2) reduced performance (tiredness, fatigue), 3) psychological impairment (including depression, anxiety, fears and cognitive decline) and 4) length of diagnostic process (comments regarding the time it took until the correct diagnosis was made). Table 2 shows the frequencies of answers for each cluster, together with a selection of the participants´ answers in their own words. Comments about the length of the diagnostic process were only provided by U.S. patients.

Coping strategies: 48.8% of patients from the U.S. and 44.4% of the German patients stated that good medical care and competent, skilled doctors were of major help in coping with Cushing's, followed by the support of family/ friends and religion (U.S.: 36.9% vs. Germany: 31.7%). Sports and hobbies (U.S.: 10.7% vs. Germany: 22.2%) as well as accepting the disease (U.S.: 9.5% vs. Germany: 25.4%) were used more often by German patients as coping strategies to deal with the disease, whereas the exchange with other patients (U.S.: 27.4% vs. Germany: 7.9%) and to obtain information

Support needs: Support was needed to a greater extent before therapy by the U.S patients (63.1%) than by the German patients (45.1%) with p=0.035. 12.7% of the German patients even stated not to have wanted further support at any time of their illness, compared to only 2.4% of the U.S. patients (p=0.024; Table 3). On the other hand, U.S. patients were more interested in support groups, in courses on illness coping, in seminars and workshops and educational offers for the family than the German patients (all p<0.05), who stated to prefer brochures (45.1% vs 20.2%, p=0.001; Table 3).

The general interest (assessed by Likert scale) in a specific support program for patients with Cushing´s was higher in U.S. patients (3.8 ± 1.10) than in German patients (3.1 ± 1.26) with p=0.001

Table 2: *Answers of the patients in regard to the question ``Which aspects of your Cushing condition bother/bothered you the most?´´ Answers were clusterd and counted. Data are presented as frequency (n) and valid percent (%).*

Variable	US (n = 84)	Germany (n = 65)
Common symptoms related to cortisol overproduction: Moon face, buffalo hump, red cheeks, bruises that wouldn´t heal, transparent skin, inability to lose weight, acne, fat belly, high blood pressure, heart racing, cardio-pulmonary effects, tachycardia, hair growth, dizziness, body pain, swelling of body/limbs, sweating	**71 (84.5)**	**34 (52.3)**
Reduced performance: Muscle weakness, muscle loss, morning insomnia, to weak and in pain to exercise, fatigue, tired all the time, low energy	**39 (46.4)**	**24 (36.9)**
Psychological impairment: Being depressed, depression, anxiety, panic attacks, nervous, scared, I felt like I was going crazy, tantrums, sexual dysfunction, feeling crummy, cognitive changes, feeling sick, neg. effects on self-confidence, having to go it a alone, angry for no reason, confused in large crowds/noisy places, felt like I was on psychotropic drugs and slipping between dimensions, was not myself and did not know why. Being cyclical, unable to predict what would be next, feeling something was very wrong, worry about residual effects on my brain. Very poor concentration, foggy brain, memory and attention issues, permanent deficits in memory, brain always racing, forgetfulness, brain didn´t work properly, memory loss	**51 (60.8)**	**43 (66.2)**
Diagnostic process: Fighting for diagnosis; the doctors inability to link all of these symptoms; was asked if I needed counseling for my obsession with my health; how long it took for a diagnosis; I suffered for years at the hand of doctors; MDs not listening and saying stupid things like I was stressed out	**8 (9.5)**	–

(Mann-Whitney-U test). 28 (33.3%) of the U.S. patients but only 11 (15.9%) of the German patients stated a very strong interest and 21 (25.0%) of the U.S patients and 15 (21.7%) of the German patients stated a considerable interest in such a program. Nine (13.0%) German and 2 (2.4%) U.S. patients expressed no interest in a support program.

In regard to specific topics that should be covered by a support program more U.S. patients than German patients wished to communicate with other patients (75.0% vs. 52.9%, p=0.006) and to learn more about stress management (60.7% vs. 33.8%, p=0.001; Table 4). 89.3% of U.S. patients would attend internet-based programs compared to 75.4% of German patients (p=0.040). There were no differences between groups for the preferred duration of and the willingness to pay for such a program, but U.S. patients would be willing to travel longer distances to attend a support meeting (p=0.027; Table 4).

DISCUSSION

To our knowledge, this is the first patient-reported survey which demonstrates the need for additional support apart from medical interventions in patients with CD or CS, although the negative long-term impact of these illnesses on health-related QoL has been confirmed in many studies [22-27]. Patients in both Germany and the USA who completed our survey reported a wide spectrum of past or present Cushing-related symptoms, psychological impairment as well as reduced physical and mental performance. In line with the high subjective illness distress, the vast majority of the participants (97% in the USA, 87% in Germany) stated that they wanted additional support at any time during the disease, most often after diagnosis and during the first year of treatment. Many of them were willing to pay for such additional support.

continued

Table 3: *Support needs of the patients. Data are presented as frequency and valid percent (%).*

Variable	US (n = 84)	Germany (n = 71)	p-Value
Stages at the course of the disease patients wished for more support (multiple answers possible)			
Before therapy	53 (63.1)	32 (45.1)	0.035
In the weeks directly after therapy	36 (42.9)	26 (36.6)	0.511
Within the first year after start of therapy	38 (45.2)	30 (42.3)	0.747
Never	2 (2.4)	9 (12.7)	0.024
Current interest in different kinds of supportive offers (multiple answers possible)			
In person support group	43 (51.2)	24 (33.8)	0.035
Webinar / Online forum	45 (53.6)	28 (39.4)	0.106
Lectures	29 (34.5)	31 (43.7)	0.253
Courses on coping with the illness	41 (48.8)	19 (26.8)	0.008
Seminars or Workshops	31 (36.9)	13 (18.6)	0.019
Leaflets / brochures	17 (20.2)	32 (45.1)	0.001
Educational offers for the family	29 (34.5)	8 (11.4)	0.001
Others††	12 (14.3)	7 (10.1)	0.472
No Interest	5 (6.0)	9 (12.9)	0.166

This snapshot is in accordance with themes discussed in focus groups of pituitary adenoma patients and conducted by a Dutch research group, where mood problems, negative illness perceptions, issues of physical, cognitive and sexual functioning were among the most prominent complaints of patients with [28] CD. Based on the feedback provided by their focus group participants, the research group developed and validated a questionnaire for pituitary patients, which aims to assess to what extent patients are bothered by consequences of the disease as well as their needs for support [29]. However, results on the practicability and usefulness of this questionnaire and the consequences drawn thereof in clinical practice are yet to be awaited.

The Dutch researchers' focus group results and the feedback given by our surveyed patients reflect unmet support needs despite receiving medical care in modern western healthcare environments. Patients with CD and CS carry the burden of their illness that often develops insidiously and may remain undiagnosed for a long time, and causes physical disfigurement and severe co-morbidities. The illness may not necessarily become controlled after surgical and/or medical intervention. Moreover, by the nature of hypercortisolism in active and hypocortisolism in treated disease, CD and CS are prone to be accompanied by mental symptoms such as depression and anxiety [30, 31]. Such a course of illness requires constant adaptation and possibly changes of patients' healthcare management to control symptoms, which can cause patients to experience stress and uncertainty [32].

In some respects, modern health care systems have already acknowledged the additional support needs of chronically ill patients. The insight, indicating that a model of care, where the patient is seen as the recipient and the physician as the giver of medical care, does not suit the needs and reality for most patients with chronic illnesses. This has led to the development of new models of care in which patients move from a passive role as healthcare recipients towards an active role as an equally important partners in the management of their illness. The Chronic Care Model (CCM) developed by Wagner et al. in 2001 [33] is such a model, according to which high-quality chronic illness

continued

Table 4: *Questions concerning educational and support programs. Data are presented as frequency and valid percent (%) or as mean ± standard deviation.*

Variable	US	Germany	p-Value
Topics for educational and support programs the patients are interested in (multiple answers possible)	**(N = 84)**	**(N = 68)**	
Communicating with other people	63 (75.0)	36 (52.9)	**0.006**
Relaxation	37 (44.0)	25 (36.8)	0.409
Nutritional advice	43 (51.2)	31 (45.6)	0.518
Stress management	51 (60.7)	23 (33.8)	**0.001**
Exercise	44 (52.4)	31 (45.6)	0.420
Health Care Bureaucracy/Financial Issues	30 (35.7)	23 (33.8)	0.865
Coping with daily hassles	31 (36.9)	21 (30.9)	0.493
Others	20 (23.8)	16 (24.2)	1.000
Type of program the patients are interested in (multiple answers possible)	**(N = 84)**	**(N = 61)**	
Internet-based program	75 (89.3)	46 (75.4)	**0.040**
In person seminars – weekend meetings	39 (46.4)	21 (34.4)	0.173
In person seminars – meetings during the week	30 (35.7)	13 (21.3)	0.068
Duration of the program	**(N = 84)**	**(N = 60)**	
Several hours	36 (42.9)	22 (36.7)	0.494
Entire day	11 (13.1)	10 (16.7)	0.634
Entire weekend	2 (2.4)	2 (3.3)	1.000[a]
Flexible timing (available through internet courses only)	35 (41.7)	26 (43.3)	0.866
How far would the patients travel to attend such an in person seminar?	**(N = 76)**	**(N = 48)**	
Miles[b]	168.0 ± 468.01	46.9 ± 49.54	**0.027**
How many patients would be willing to pay for a support program?	**(N = 84)**	**(N = 59)**	
Yes	51 (60.7)	31 (52.5)	0.391
No	33 (39.3)	28 (47.5)	
How much would the patients be willing to pay for a support program?	**(N = 48)**	**(N = 30)**	
Dollar	150.9 ± 243.35	100.7 ± 196.31	0.501
Euro	137.0 ± 220.81	91.3 ± 178.13	0.501

[a] *Fisher´s exact test.*

[b] *1 mile=1.609 kilometers*

care involves collaborative, productive interactions between active and well-informed patients and multidisciplinary teams of healthcare providers on the topics of illness assessment, optimization of therapy and follow-up as well as self-management support [34]. It has been estimated that 70–80% of people living with chronic illness could reduce their illness burden and costs by appropriate self-management [35]. For such reasons, the improvement of patients' abilities in the self-management of their illness is a major component of patient support programs. Such programs have already been implemented for patients with cancer, multiple sclerosis, diabetes mellitus, chronic back pain and other diseases [18, 19, 36-42]. Many of these programs are well received by the respective patient populations and have demonstrated a high degree of effectiveness in terms of better health outcomes, QoL and functional status [43-45]. A recent definition of health has even acknowledged the importance of self-management by defining health as 'the ability to adapt and self-manage in the face of social, physical, and emotional challenges' [46].

The multitude of reported positive effects, ranging from improved clinical and psychosocial outcome over better adherence and self-management to decreased health care costs, encourages the development of specific support programs for CD/CS [17, 47, 48]. However, in the case of CD and CS the development of special programs devoted solely to this patient group are likely to be cost-intensive and, due to the rareness of the disease, beneficial to only very few patients. Yet, despite the unique features of their illness, patients with Cushing's do not differ in all respects from other patients with chronic conditions such as heart disease, multiple sclerosis or diabetes. Common challenges associated with the management of such conditions include dealing with symptoms and disability, managing complex medication regimes, having to make lifestyle changes, maintaining a proper diet and exercise, adjusting to psychological and social demands and to engage in effective interaction with their health care professionals. A study by our group has shown that negative coping strategies are a major determinant of poor QoL, depression and embitterment in patients with CD [10]. Since many techniques like learning adaptive coping strategies, rules for healthy nutrition or basic exercises are universally useful, the adaption of already existing programs from other diseases might be a sensible first step for the establishment of self-management programs for patients with Cushing's.

Such an effort has already been made for patients with pituitary disease in general, by a Dutch research group, who implemented and evaluated a Patient and Partner Education Programme for Pituitary Disease (PPEP-Pituitary) (33). They found positive effects of this program in patients and partners and concluded that future research should focus on the refinement and implementation of such a self-management program into clinical practice.

Our results suggest that such a program should focus on the time before and first year after treatment, which due to the sudden cortisol deprivation is severely stressful for the patient. Topics worth covering might be communication, nutritional advice and exercise, since these are the topics most frequently requested in both countries. Stress management seems to be of interest especially to U.S. patients. Also, the setting should be adapted to cultural preferences. In the USA, in-person support groups are highly desired with patients willing to travel considerable distances and pay for such programs, while German patients seem to prefer written information in leaflets or brochures. Patients in both countries express interest in web-based forms of support.

Last but not least, our results underline the importance of patient support groups that are already in place. Already a quarter of the U.S. patients report, that the exchange with other patients was most helpful to them. Nevertheless, 50% express a wish for more patient support groups. It can be speculated, that some patients might not know about already existing groups. Oftentimes it might already improve a patient's wellbeing to ensure that he has access to all the existing support like support groups or information material.

One limitation of the present study is that the use of patient response tools such as a PRO survey may have introduced a bias as it can be speculated that patients with a higher disease burden are more likely to participate in a survey querying disease symptoms and need for support. Nevertheless, the results must be understood as a call to identify, implement and evaluate valid support programs with an emphasis of self-management for patients with Cushing's and other endocrine diseases, preferably in a multi-center setting. Culture-specific support needs should also be taken into account.

CONCLUSION

Patients with Cushing's in the USA and Germany need competent physicians and long-term medical care in dealing with the effects of CD/CS, but also request additional support besides medical interventions, while the interest in specific topics addressed in support programs differs somewhat between patients of both countries. The latter implies that not only disease-specific but also culture-specific training programs would need to be considered to satisfy the needs of patients in different countries.

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Marked Response of a Hypermutated ACTH-Secreting Pituitary Carcinoma to Ipilimumab and Nivolumab

Lin AL, Jonsson P, Tabar V, Yang TJ, Cuaron J, Beal K, Cohen M, Postow M, Rosenblum M, Shia J, DeAngelis LM, Taylor BS, Young RJ, Geer EB. Journal of Clinical Endocrinology and Metabolism. 2018 Oct 1;103(10):3925-3930. doi: 10.1210/jc.2018-01347

In this case, a 40-year-old female with Cushing's was being treated at Memorial Sloan Kettering Cancer Center (MSK) in NYC for an aggressive ACTH-secreting pituitary carcinoma. She had tried several treatments including multiple surgeries, radiation, and chemotherapy. It had metastasized to her liver, and the pituitary tumor was producing ACTH at extremely high levels – 45,550 pg/mL at its worst, with a normal high level being 50 pg/ml.

Dr. Eliza Geer and her team at MSK had noticed that patients receiving a type of immunotherapy called checkpoint inhibitors for other types of cancers frequently had pituitary inflammation as a side effect of the therapy. Checkpoint inhibitors work by removing a cancer cell's "brake" on the immune cell that prevents it from destroying the cancer. The doctors at MSK postulated that the treatment must be targeting proteins in the pituitary cells, and that made them think that this type of therapy might have some effect on pituitary tumors. The patient in this case had amazing shrinkage of both her pituitary and liver tumors on the two-drug therapy.

This is the first reported use of immunotherapy to treat pituitary tumors. In addition to that result, samples of the patient's tumors were taken and analyzed for gene mutations: the pituitary tumor before she received chemotherapy, and the liver tumor after chemo. The liver tumor had many mutations that the pituitary tumor did not. This led the researchers to consider that the hypermutation of the original tumor cells was perhaps caused by the chemo and that mutated tumors might be more responsive to immunotherapy.

This case has led the team at MSK to embark on a clinical trial in hopes of good response to this type of treatment for pituitary tumors. The patient is doing better and currently only takes one form of checkpoint inhibitor immunotherapy. For the full story, some impressive photos of tumors before and after treatment, and an excellent short video about how immunotherapy works, scan the QR code or visit https://www.mskcc.org/blog/case-study-gives-hope-clinical-trial-testing-immunotherapy-aggressive-pituitary-tumors.

Bilateral Adrenalectomy in the 21st Century: When to Use it for Hypercortisolism?

Carole Guerin, David Taieb, Giorgio Treglia, Thierry Brue, André Lacroix, Frederic Sebag, Frederic Castinetti. Society for Endocrinology. 2016 February, Volume 23, Issue 2. doi: 10.1530/ERC-15-0541

The purpose of this study was to examine existing treatments and outcomes for a variety of pituitary, adrenal, and ectopic tumors in comparison to treatment with a bilateral adrenalectomy (BLA). Two major sources of research and other medical literature from 1950 through 2015 were searched using six related terms. The results were analyzed with specific highlight on outcome and recurrence rates. The authors feel that advances in treatments for Cushing's, especially over the last decade or so, should cause endocrinologists to consider all options ahead of BLA if appropriate for the patient.

BLAs were first performed through open surgery (anterior laparotomy), then by opening the back and removing the 12th rib (posterior approach), and finally the laparoscopic method that is used today and generally considered the gold standard. Current Endocrine Society guidelines on diagnosis and treatment of Cushing's do not recommend BLA as a first line of treatment. Efficacy of the various pharmaceutical options and radiation as first or second line treatments are well documented in medical literature, but the authors also wanted to look at when BLA is an appropriate choice. One of the things they found was that side-by-side comparisons are virtually non-existent. Also complicating things is that there is not enough follow up data on patients past approximately 10 years.

BLA in Acute Hypercortisolism: Because long-term exposure to high levels of cortisol causes complications that are not completely reversible after treatment, the goals are earlier diagnosis and faster control of symptoms. The more severe the hypercortisolism, the more life-threatening it becomes, especially in patients with psychiatric symptoms. The literature points to BLA not always being a good option for patients with severe symptoms; instead it seems to point at fast-acting medication that can rapidly lower cortisol but also be adjusted after cortisol control has been achieved. Monitoring the various drugs available to Cushing's patients is challenging for doctors and seems to be best suited to expert centers with the knowledge and resources to follow those patients closely and act quickly based on response to medication.

BLA in Chronic Hypercortisolism: Pituitary surgery for Cushing's Disease is the first line of treatment with an immediate remission rate of 50-80%. Failed surgery leads to additional choices to make – another surgery, radiation, and/or medication. BLAs do get recommended under certain circumstances, for example to achieve the "final cure" in patients with multiple failed treatments or patients who are not able to comply with a drug regimen. Even though a BLA seems fail-proof, there are cases in which patients have experienced recurrence of their hypercortisolism even after having their adrenals removed.

Comparison with Long-Term Treatment with Medical Therapy: The authors focused on data related to the efficacy and tolerance of medical therapy. They found that overall there is evidence that medical therapies are a safe option and can be maintained on a long-term basis. Their benefit over BLA is that they do not cause permanent adrenal insufficiency. There are situations where a BLA might still be the better option; examples include a young woman who would like to get pregnant and a patient who cannot comply with dosing requirements.

Comparison with New Radiotherapy Modalities: Most studies were based on the Gamma Knife, but the authors felt that similar results would be seen with other forms. The main advantage of radiation is that the target is clearly defined. A drawback could be the time it takes to start to see its effects, which is estimated to be 2-4 years. Patients almost always need medical therapy as a "bridge" while waiting for the radiation to work. Even so, the low rate of side effects makes radiation a desirable option for some patients who also have success with one of the medical options available. In the event that radiation doesn't work, BLA remains an option.

The review concludes that BLA is the most effective definitive treatment for hypercortisolism when surgical removal of the source isn't possible. However, several options exist that can change this narrow path for patients who find themselves in experienced hands. Defining the place of BLA in 21st century hypercortisolism treatment is a challenge that will only get more complex as new drugs currently in the works become available. These additions to the medicine cabinet are likely to encourage more "wait and see" approaches instead of turning so quickly to BLA. There are also improvements in radiological methods that are increasing the chances of finding small endocrine tumors in the first place which will hopefully contribute to a shortened average diagnosis time.

On-line Tools for Symptom Tracking

Symptom tracking can be useful for gauging your recovery or determining when to test if cyclic Cushing's is suspected. A symptom tracking application from Corcept, maker of Korlym, is available here: *www.cushingsconnection.com*

High Cortisol is Not Always Cushing's

Editor's Note: This patient story originally appeared in our Summer 2016 issue. We contacted Mona recently to see how she is doing now; her update follows her original story.

In 2004, I decided it was time to lose weight. I lost 100 pounds in a year on a low-carb diet. I felt fantastic. Then, I started feeling sick. My doctor recommended adding more carbs to my diet. I added mostly vegetables and fruit, but the weight began creeping back up. I removed all fruit, and later went back to full low-carb (no fruits or vegetables) and my weight still went up. I was eating healthier and exercising every day and my weight was still going up. By 2008, I had gained back the 100 pounds and then some. In desperation, I went to an endocrinologist to figure out what was wrong with my metabolism. He checked my thyroid, which was fine, and then told me to eat less and exercise more. I was mortified. I cried all the way home because I knew that I was already doing the best I could.

I tried many different diets over the next few years and all types of exercise regimens and still no results. I saw other endocrinologists who also dismissed me. One told me that I was morbidly obese and I would get diabetes if I didn't lose weight. He also said exercise and eat less. Ugh not again. I was getting nowhere fast.

By 2014, I had many health issues and no explanations. I was getting rashes that wouldn't go away. I was getting depressed because I was losing hope. I was very tired and could barely function. I was bruising easily and slow in healing. I went from doctor to doctor with no results. At the end of 2014, I went to an allergist about my rashes. Since there was no visible rash at my appointment, I asked him if my inability to lose weight could be related to food allergies. He stated that food allergies typically cause a person to be very sick and throw up. He mentioned that some people with food sensitivities have difficulty losing weight and gave me an article on that subject.

I eagerly read the article and it made sense. I began an anti-inflammatory diet called "The Plan" to identify food sensitivities by introducing highly sensitive foods one at a time. I lost 30 pounds in 2 months, then plateaued. I worked with a naturopathic doctor affiliated with "The Plan". She tried several things: lowering my histamine levels by taking MSM (a sulfur compound), building my immunity through probiotics, and addressing my yeast overgrowth. Nothing worked: my weight would not budge. In April 2015, I went to a local naturopathic doctor, who was understanding and believed that I was eating right and exercising daily. She decided to do hormone tests, including a cortisol test. My cortisol levels were 10 times higher than they should be at night. Another in-depth cortisol test confirmed my cortisol was out of control at night. She explained that she believed I had Cushing's syndrome and that I needed to see an endocrinologist.

I made an appointment and waited four months to see the endocrinologist. The endocrinologist dismissed the tests because a naturopathic doctor ordered them. She refused to do further testing for Cushing's. I can't begin to describe my frustration. I left another doctor's office crying. This was becoming a pattern.

Luckily, I am persistent and sent my cortisol results to another endocrinologist for a second opinion. This doctor suggested more tests, but she was in California and I live in South Carolina. Most endocrinologists in my area were not taking new patients, but I found one two hours away.

A few weeks later, I went to this new endocrinologist with my cortisol results in hand. She was wonderful. She sensed my stress, took my hand and said, "Don't worry; we will figure out what is going on." She wanted to find out why my cortisol levels were only out of range at night and early morning. She recommended a sleep study to see if I had sleep apnea. She explained that sleep apnea can cause cortisol levels to rise because your body is stressed when you are not breathing at night. And when your cortisol levels are high, you can't lose weight.

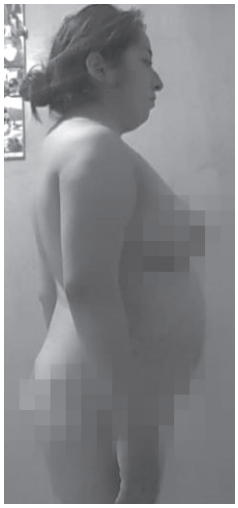
Two weeks later, I had a sleep study that showed I have moderate sleep apnea. My oxygen levels dropped below 60% at night (it should be above 90%). Two weeks later, I had a second sleep study to set the proper air pressure level that I need. By November 2015, I had my CPAP (continuous positive airway pressure). My quality of life has improved significantly. The weight is coming off consistently now, the rashes are gone, my hair is growing back in, the depression is gone, and I am healing a lot faster. God is good!

I am telling my story because not all cases of elevated cortisol are due to a tumor. Sometimes there is another reason for high cortisol, and you need to take the time to figure it out. I am just glad that God guided me to the right answer for me.

Mona L. Loris, SC, monap@sccoast.net

We asked Mona for an update, and she said: I am doing great. I can't believe how much better I feel since I started using my CPAP. My cortisol levels are all back to normal and all of my symptoms have vanished. I had been getting progressively worse for two years before the doctors finally figured out what was going on. In retrospect, it should have been one of the first things they suspected.

Before Cushing's



With Cushing's

I never considered myself vain enough to pursue beauty regimens with the aim of improving my physical appearance. I'm 28 years old, single, without kids. However, a number of physical things led me to a dermatologist in August 2018: stitches from injuries sustained in falls that did not heal, I bruised very easily and they were slow to disappear, and I had aggressive acne on my face as well as deep red stretch marks on my stomach. I attributed these to sudden weight gain. This dermatologist was the one who diagnosed me with likely Cushing's syndrome. Without alarming me, he told me to see an endocrinologist. I read on the Internet about this rare disease and everything was consistent with what they described as symptoms.

I thought back and realized that my symptoms probably started two years prior to this moment with sudden weight gain and amenorrhea that I thought was due to my contraceptive method. I felt like I was killing myself in the gym and with a strict diet, but I did not manage to lose weight. In fact, the opposite – it continued to rise (12 kilograms in a year) along with other symptoms: acne, red stretch marks, loss of libido, chronic tiredness, high thirst, loss of vision, sensitive skin, bruising, difficult scarring, osteoporosis, high blood pressure, the famous moon face, excessive hair growth, and irritability. I could not do yoga, or ride a bicycle, or go to the gym. I was transforming quickly and I visited several specialists – gynecologists, gastroenterologists, and nutritionists - wanting to correct my bulging stomach. They even sent me pregnancy tests and I was diagnosed with gastritis, but no one figured out that Cushing's was the cause for my symptoms.

When I finally went to the endocrinologist, he sent me to do studies to confirm or rule out this disease. We started with a 3T MRI and multiple blood tests - cortisol, sodium, potassium, hormones, thyroid. Unfortunately, all the studies were positive. Being honest, the doctor explained to me that the costs of treatment and surgery in the private sector would be very high, so he sent me to the Neurology and Neurosurgery Institute of Mexico City. He felt that this specialized hospital would be the best choice in the country to treat me.

I started the disease research protocol to be a candidate for surgery. I went through more cortisol tests - urine, dexamethasone, saliva, blood, and additional MRI, hormones, glucose, cholesterol, and thyroid. The most painful was the invasive catheterization IPSS, even with local anesthesia.

My surgery was on December 4, 2018. I expected to be discharged five days later, but things were complicated. I ended up with a CSF leak, so I was admitted to do studies again to locate where I had the leak and how they were going to repair it. Even though this is a fairly common risk with surgery, I was in the hospital for nine days so the doctors could seal the leak with a skin patch from my leg.

My mood was about as low as it could get, I had tubes coming out from all over my body, and the most painful was a lumbar drain to relieve pressure from the new leak patch. My veins were thin and weak but they still needed to take blood every 4 hours to monitor sodium and cortisol levels, in addition to two daily gasometries. They were hell.

A day after the procedure to repair the CSF leak, my face went numb. I told the nurses and the doctor in charge. However, they had other priorities, and the next morning, I woke up with fever; a few minutes later I slipped into a coma. I remember it as if it were a nightmare: I heard the doctors argue, they approached me and thumped me on the chest, it hurt, but I could not react, my mother was hysterical with the doctors. I heard that my condition was low cortisol or probably an infection in the brain, my head hurt a lot, it was hot and then cold, there was no way to react and say what I felt, a nurse gave me an injection in the stomach, I did not understand anything, I cried in pain and prayed to God to enlighten my mother. I had underestimated the surgery, I had read only successful cases without complications, but mine was not one of those.

I woke up after 32 hours of unconsciousness still with a headache, and I asked for the doctor. I vomited regularly until some of the tubes were eventually removed.

I think recovery is the hardest part of all this. I cannot walk, I cannot breathe, I shake, and I sneeze. I know my body will slowly get stronger again, and this is what gives me encouragement – that all the symptoms will be gone soon, and I will lose weight. My vision has improved and the acne is gone, the stretch marks are lighter, my memory and concentration are better and I'm recovering. I understand that healing can mean more than curing a disease, it means learning to live with it.

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