Dilemmas in pituitary disease management during the COVID-19 era: How should clinicians adapt to the changing clinical environment?

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Disclosures

Prof. Fleseriu

- Grants to University /scientific consultancy with Chiasma, Crinetics, Ionis, Ipsen, Novartis, Pfizer and Strongbridge

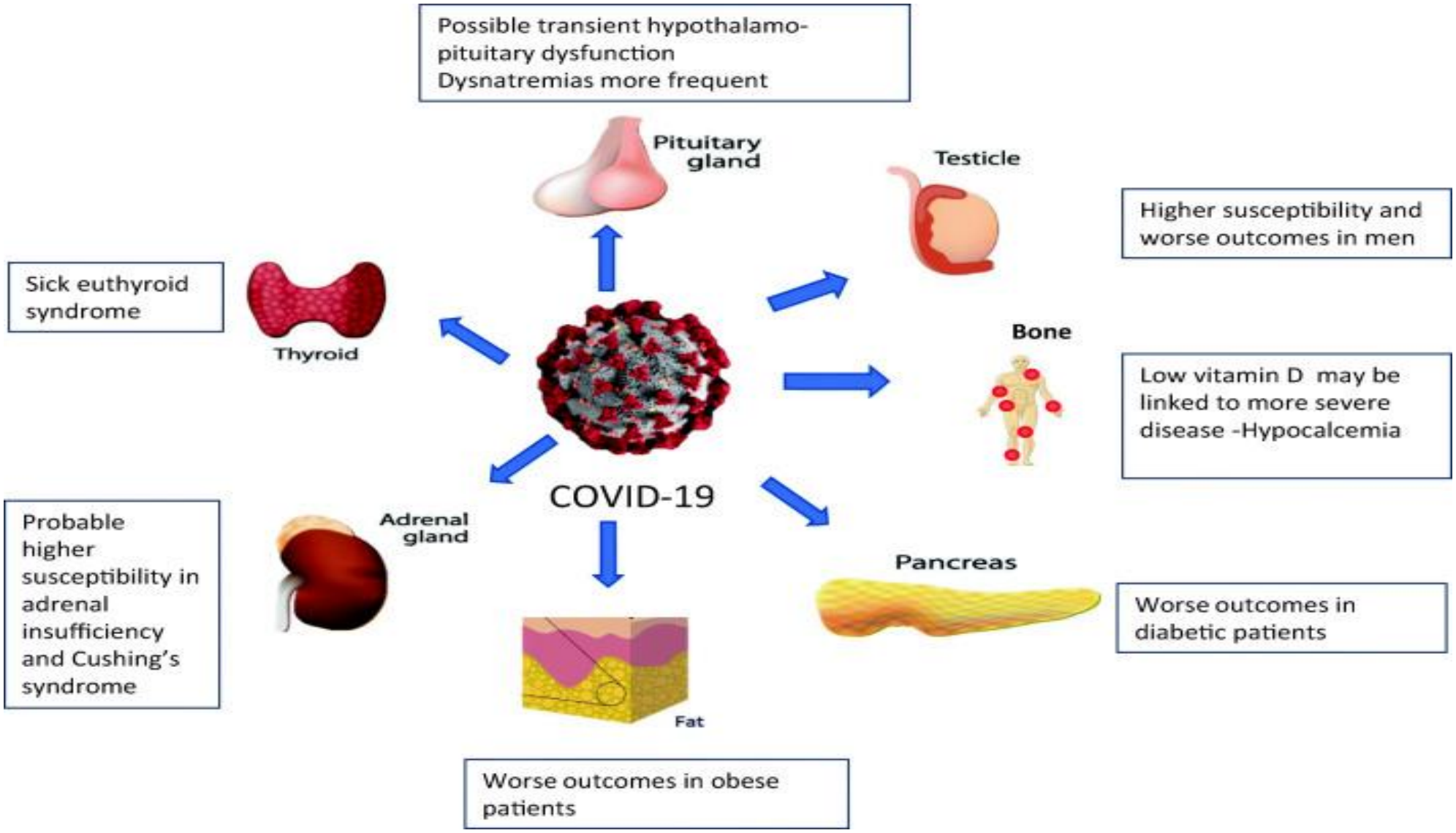
Prof. Giustina

- Grants/consultancy with Abiogen, Astellas, Ipsen, Novartis and Pfizer

Agenda

16:30 – 16:35 (5 mins)	**Welcome, introductions and agenda**	**M. Fleseriu & A. Giustina**
16:35 – 16:55 (20 mins)	Non-functioning pituitary adenoma with visual loss and hypopituitarism during the COVID-19 pandemic	M. Gurnell
16:55 – 17:15 (20 mins)	Acromegaly during the COVID-19 pandemic	N. Karavitaki
17:15 – 17:35 (20 mins)	Cushing's disease during the COVID-19 pandemic	A. McCormack
17:35 – 18:00 (25 mins)	Case study discussion and Q&A	Chaired by: M. Fleseriu & A. Giustina

COVID-19 has multiple effects on the endocrine system



Marazuela M, Giustina A et al. Rev Endocr Metab Disord. 2020. doi: 10.1007/s11154-020-09569-2

Management of pituitary tumours in 2020

- Typically involves a multidisciplinary care team and can represent a management challenge[1,2]

- The COVID-19 pandemic has put on-hold routine medical care for hundreds of millions of patients worldwide[2]
    - For pituitary disorders, this includes disruptions to pituitary surgery and limited access to care and testing (laboratory and radiological)[1]
    - Reduced access to routine clinical services means that some patients with confirmed/suspected pituitary disease are facing delays in diagnosis and implementation of treatment[1]

1. Fleseriu M, et al. Pituitary. 2020. doi: 10.1007/s11102-020-01059-7
2. Fleseriu M, et al. Eur J Endocrinol. 2020; 183:G17–G23

Modified management approach: regular/routine monitoring

Stratify patients risk	• MDT assessment of risk to guide intensity of monitoring and allowing appropriate delivery of care in the COVID-19 pandemic
Collaboration	• Collaborate with administration and management for appropriate prioritisation of resource and appointments and smooth delivery of care (e.g. virtual clinics)
Patients who are well-controlled or in remission	• Virtual clinics can be conducted in these patients • No change of treatment regimen for 6 months unless there is strong clinical suspicion of clinical changes

MDT, multidisciplinary team

Fleseriu M, et al. Eur J Endocrinol. 2020; 183:G17–G23

Objectives

Improve the management of the following conditions during the COVID-19 pandemic:

- Non-functioning pituitary adenoma with visual loss and hypopituitarism
- Acromegaly
- Cushing's disease

Our speakers

Ann McCormack
Garvan Institute of Medical Research,
New South Wales, Australia

Mark Gurnell
Cambridge University Hospitals
NHS Foundation Trust, UK

Niki Karavitaki
University Hospitals Birmingham
NHS Foundation Trust, UK

Non-functioning pituitary adenoma with visual loss and hypopituitarism during the COVID-19 pandemic

Mark Gurnell

UNIVERSITY OF CAMBRIDGE

NHS
Cambridge University Hospitals
NHS Foundation Trust

Welcome Trust-MRC Institute of Metabolic Science

Disclosures

- None to declare

Clinical case – presentation

Late March 2020

44-year-old man

Presentation: visual loss

- hazy peripheral vision since Sept 2019
- recent significant deterioration
- no other symptoms

- no relevant past medical history
- no regular medications

- nil else of note

Clinical examination

- Visual acuity:
  - right 6/9
  - left 6/18

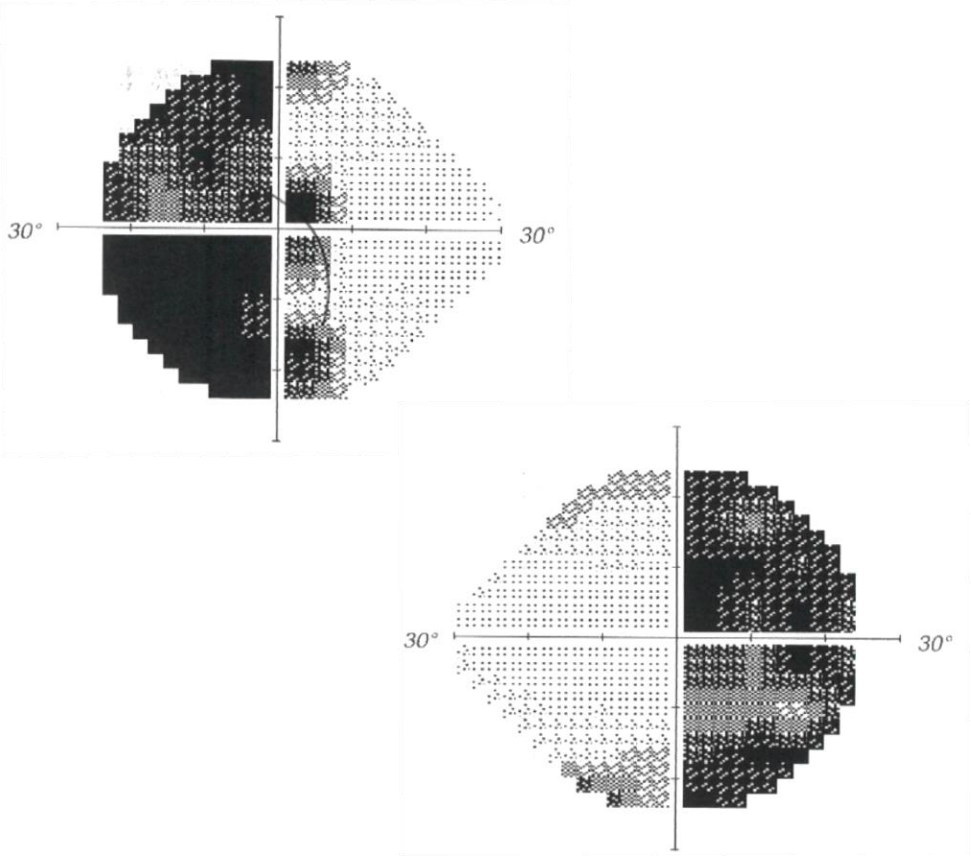
- Bilateral loss of colour vision

- Bitemporal hemianopia

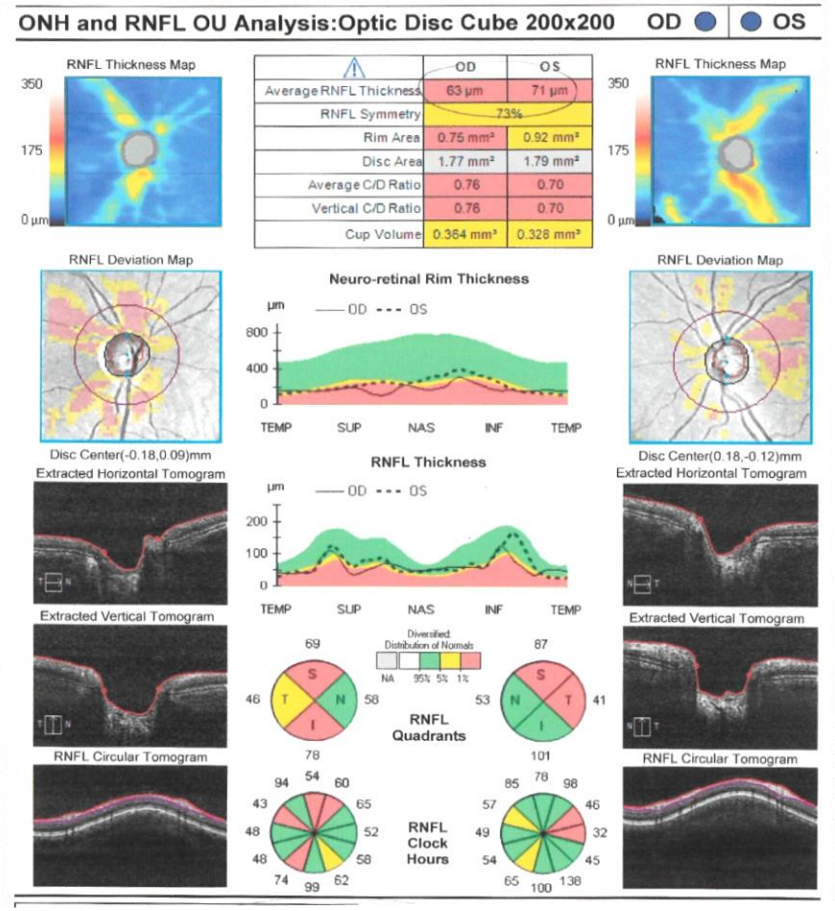
- No stigmata of endocrine dysfunction

Clinical case – ophthalmology

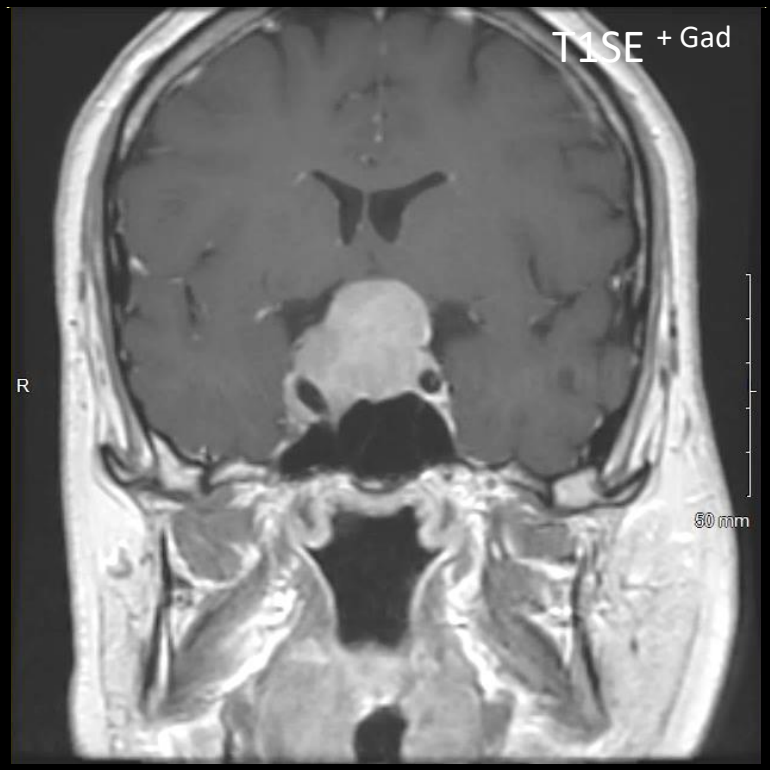
Visual fields

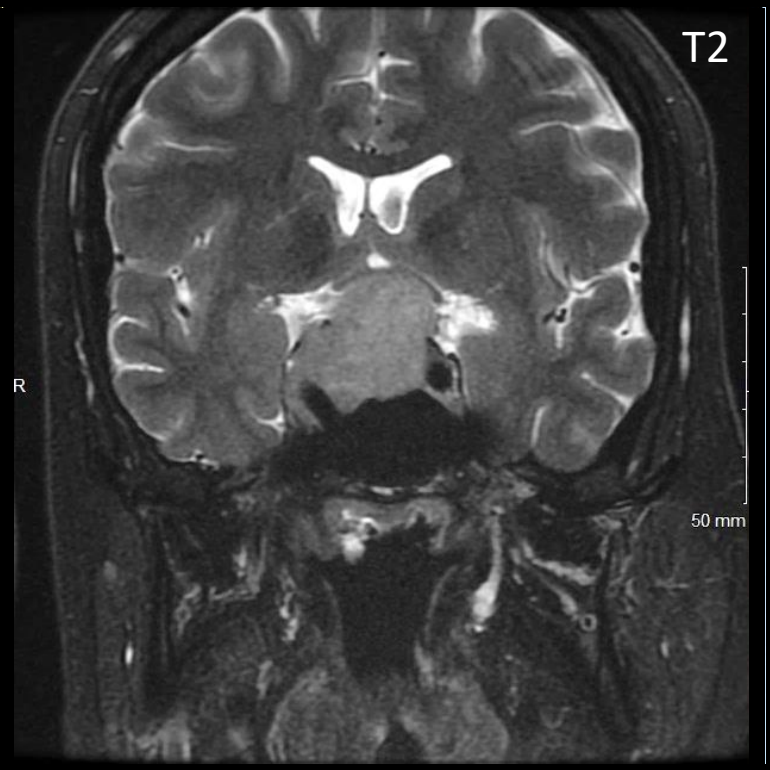


Optical Coherence Tomography



Clinical case – pituitary MRI





Clinical case – endocrinology

9AM profile

Investigation	Result	Reference Range
Cortisol	523	200–550 nmol/L
Free T4	9.7	10.0–21.0 pmol/L
TSH	1.18	0.35–5.5 mU/L
Prolactin	821	45–375 mU/L
LH	2.6	1.5–6.3 U/L
FSH	3.8	1.0–10.1 U/L
Testosterone	6.2	7.2–31.3 nmol/L
IGF-1	19.0	11.6–31.3 nmol/L

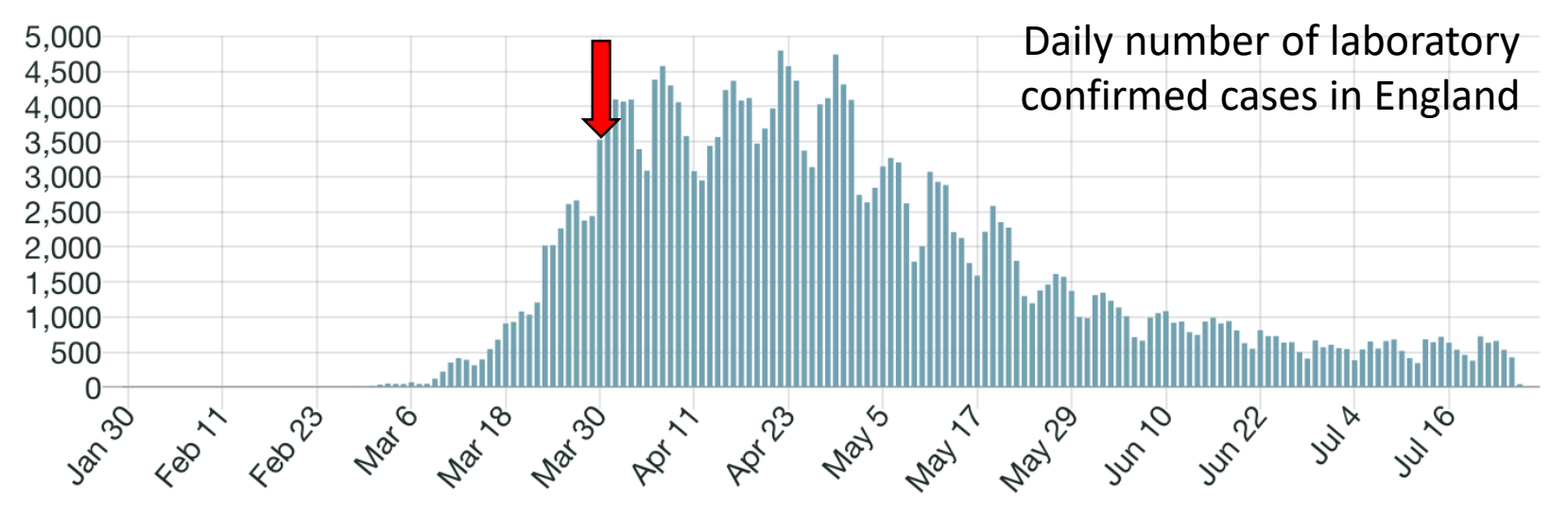
FSH, follicle stimulating hormone; IGF-1, insulin-like growth factor 1; LH, luteinising hormone; T4, thyroxine; TSH, thyroid stimulating hormone

Dilemmas

1. Wait or intervene surgically?

2. Transsphenoidal approach or craniotomy?

CONTEXT



https://coronavirus.data.gov.uk

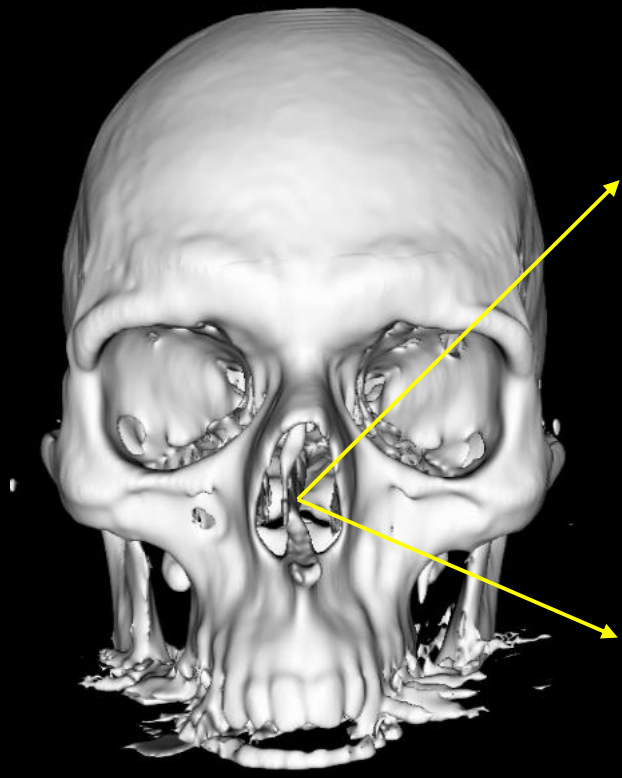
TSS – pros and cons…

TSS approach

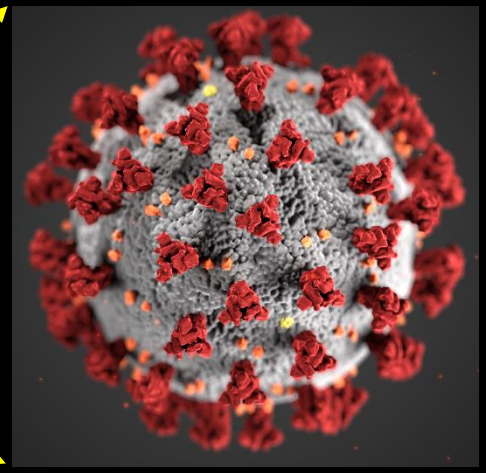
Compared with craniotomy:

- less traumatic direct route to sella
- avoidance of brain retraction
- lower morbidity and mortality

Standard of care since 1980s



Courtesy of Dan Gillett



Center for Disease Control & Prevention

TSS, transsphenoidal surgery

Solari D, et al. Handbook of Clinical Neurology. 2014; 124:291–301

Social media and rapid on-line publications…

19 March 2020

DrJFM - Juan C. Fernandez-Miranda MD -
@drjfm_stanford

One of the first large outbreaks of #COVID19 in Wuhan was after #endoscopicendonasalsurgery for #pituitaryadenoma. 14 health care providers involved in the case got infected, several died. This is very serious. Be safe @drjfm_stanford

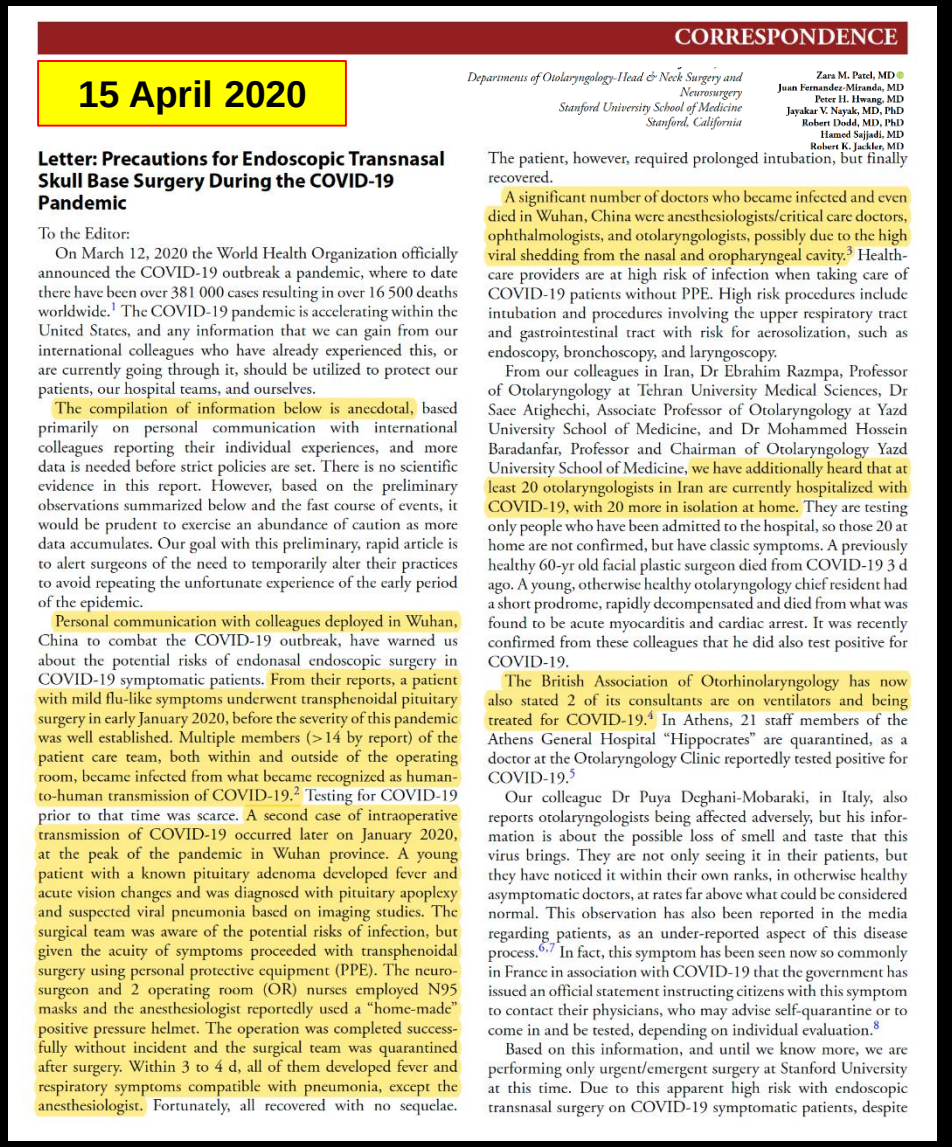
12:12 AM · Mar 19, 2020 from Palo Alto, CA · Twitter for iPhone

50 Retweets **56** Likes

Hani Marcus @hani_marcus · Mar 19
Replying to @drjfm_stanford
Thanks @drjfm_stanford - this is very important information - may I ask the source before we disseminate locally?

Antonios El Helou @ELHELOUA · Mar 19
Replying to @drjfm_stanford
Thank you for sharing, can you share the source please?

Theodore Schwartz MD @TedSchwartz13 · Mar 20
Replying to @drjfm_stanford
Just did a case today. We are getting her tested. Fingers crossed. She's asymptomatic so hopefully not an issue but thanks for the heads up. Just got called about an apoplexy case! Trying to balance patient versus staff well-being with inadequate N95s.



15 April 2020

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Letter: Precautions for Endoscopic Transnasal Skull Base Surgery During the COVID-19 Pandemic

To the Editor:

On March 12, 2020 the World Health Organization officially announced the COVID-19 outbreak a pandemic, where to date there have been over 381 000 cases resulting in over 16 500 deaths worldwide.[1] The COVID-19 pandemic is accelerating within the United States, and any information that we can gain from our international colleagues who have already experienced this, or are currently going through it, should be utilized to protect our patients, our hospital teams, and ourselves.

The compilation of information below is anecdotal, based primarily on personal communication with international colleagues reporting their individual experiences, and more data is needed before strict policies are set. There is no scientific evidence in this report. However, based on the preliminary observations summarized below and the fast course of events, it would be prudent to exercise an abundance of caution as more data accumulates. Our goal with this preliminary, rapid article is to alert surgeons of the need to temporarily alter their practices to avoid repeating the unfortunate experience of the early period of the epidemic.

Personal communication with colleagues deployed in Wuhan, China to combat the COVID-19 outbreak, have warned us about the potential risks of endonasal endoscopic surgery in COVID-19 symptomatic patients. From their reports, a patient with mild flu-like symptoms underwent transphenoidal pituitary surgery in early January 2020, before the severity of this pandemic was well established. Multiple members (>14 by report) of the patient care team, both within and outside of the operating room, became infected from what became recognized as human-to-human transmission of COVID-19.[2] Testing for COVID-19 prior to that time was scarce. A second case of intraoperative transmission of COVID-19 occurred later on January 2020, at the peak of the pandemic in Wuhan province. A young patient with a known pituitary adenoma developed fever and acute vision changes and was diagnosed with pituitary apoplexy and suspected viral pneumonia based on imaging studies. The surgical team was aware of the potential risks of infection, but given the acuity of symptoms proceeded with transphenoidal surgery using personal protective equipment (PPE). The neurosurgeon and 2 operating room (OR) nurses employed N95 masks and the anesthesiologist reportedly used a "home-made" positive pressure helmet. The operation was completed successfully without incident and the surgical team was quarantined after surgery. Within 3 to 4 d, all of them developed fever and respiratory symptoms compatible with pneumonia, except the anesthesiologist. Fortunately, all recovered with no sequelae. The patient, however, required prolonged intubation, but finally recovered.

A significant number of doctors who became infected and even died in Wuhan, China were anesthesiologists/critical care doctors, ophthalmologists, and otolaryngologists, possibly due to the high viral shedding from the nasal and oropharyngeal cavity.[3] Healthcare providers are at high risk of infection when taking care of COVID-19 patients without PPE. High risk procedures include intubation and procedures involving the upper respiratory tract and gastrointestinal tract with risk for aerosolization, such as endoscopy, bronchoscopy, and laryngoscopy.

From our colleagues in Iran, Dr Ebrahim Razmpa, Professor of Otolaryngology at Tehran University Medical Sciences, Dr Saee Atighechi, Associate Professor of Otolaryngology at Yazd University School of Medicine, and Dr Mohammed Hossein Baradanfar, Professor and Chairman of Otolaryngology Yazd University School of Medicine, we have additionally heard that at least 20 otolaryngologists in Iran are currently hospitalized with COVID-19, with 20 more in isolation at home. They are testing only people who have been admitted to the hospital, so those 20 at home are not confirmed, but have classic symptoms. A previously healthy 60-yr old facial plastic surgeon died from COVID-19 3 d ago. A young, otherwise healthy otolaryngology chief resident had a short prodrome, rapidly decompensated and died from what was found to be acute myocarditis and cardiac arrest. It was recently confirmed from these colleagues that he did also test positive for COVID-19.

The British Association of Otorhinolaryngology has now also stated 2 of its consultants are on ventilators and being treated for COVID-19.[4] In Athens, 21 staff members of the Athens General Hospital "Hippocrates" are quarantined, as a doctor at the Otolaryngology Clinic reportedly tested positive for COVID-19.[5]

Our colleague Dr Puya Deghani-Mobaraki, in Italy, also reports otolaryngologists being affected adversely, but his information is about the possible loss of smell and taste that this virus brings. They are not only seeing it in their patients, but they have noticed it within their own ranks, in otherwise healthy asymptomatic doctors, at rates far above what could be considered normal. This observation has also been reported in the media regarding patients, as an under-reported aspect of this disease process.[6,7] In fact, this symptom has been seen now so commonly in France in association with COVID-19 that the government has issued an official statement instructing citizens with this symptom to contact their physicians, who may advise self-quarantine or to come in and be tested, depending on individual evaluation.[8]

Based on this information, and until we know more, we are performing only urgent/emergent surgery at Stanford University at this time. Due to this apparent high risk with endoscopic transnasal surgery on COVID-19 symptomatic patients, despite

Patel ZM, et al. Neurosurgery. 2020; 87:E66–67

Social media and rapid on-line publications…

17 April 2020

In Reply: Precautions for Endoscopic Transnasal Skull Base Surgery During the COVID-19 Pandemic

To the Editor:

COVID-19 has been spreading all over the world over the past 2 mo.[1] Owing to the striking increase of COVID-19 cases, the safety of medical workers is a concern.[2] Because the virus exists in all parts of the respiratory tract, there is a heated discussion on the timing of surgical treatment of respiratory diseases, especially the safety assessment of endoscopic transsphenoidal surgery in the department of neurosurgery.

Recently, Patel et al[3] submitted an article titled "Precautions for Endoscopic Transnasal Skull Base Surgery During the COVID-19 Pandemic" to remind the neurosurgeon and otolaryngologist to pay attention to the extended endoscopic skull base surgery of patients with COVID-19. In the article, Patel et al[3] cited the co-occurrence of 14 COVID-19 infected medical workers and a COVID-19 affected patient with pituitary adenoma who underwent endoscopic transsphenoidal surgery in our department, and stated the safety issue about the transsphenoidal surgery in this emerging COVID-19 situation. However, what was described does not accord with the facts.

The first argument is about the sentence "multiple members (>14 by report) of the patient care team, both within and outside of the operating room, became infected from what became recognized as human-to-human transmission of COVID-19". It is not accurate. At the early stage of the COVID-19 outbreak, we had 1 patient who underwent endoscopic transsphenoidal surgery on January 6, 2020 and was diagnosed with COVID-19 13 d later. Among the infected medical workers, 10 nurses and 4 neurosurgeons were diagnosed and only 4 nurses contacted the COVID-19 patient directly.

The second problem is that the authors[3] believed that all the medical workers who participated in the surgery were infected, especially from the experience of the second case that the author cited, for which we have no exact information in Wuhan neurosurgery medical system. However, according to our retrospective survey on our case, none of medical staff who participated in surgery were diagnosed with COVID-19 until March 31, 2020. Today, all the infected medical staff have recovered. More importantly, the medical workers diagnosed with COVID-19 in our department later were the staff who were outside the operation room. As for the infected neurosurgeon in our department, it's conceivable to be deemed as postoperative transmission rather than intraoperative transmission.

Finally, the opinion that the authors[3] delivered should be carefully assessed. The reason why the neurosurgeon and otolaryngologist were infected needs more data to illustrate. According to the whole infection event that we experienced, we have some facts and experiences to share with the medical community.

The reason why the infection event happened in our department at the early stage is due to little knowledge about COVID-19 and insufficient protective measures. Besides, the frequently interaction between medical workers in our department promoted transmission. Thus, accumulating information about the COVID-19 should be elucidated and reducing contact between people is a necessary means to prevent the spread of the virus.

In this infection event, more nurses were infected than surgeons, because nurses and patients are in direct contact, such as in daily medical care. So, compared to droplet transmission, contact transmission may be an important factor of transmission in medical workers which more likely we ignored at the early stage. Therefore, it is very important to wash hands and clean the surface of objects in wards and living areas. What's more, it is vital to make sure that once COVID-19 patients are confirmed, strict isolation measures must be taken as soon as possible.

As for the transsphenoidal surgery, Patel et al[3] believe that aerosol droplets coming from the endonasal surgery will increase the possibility of infection of medical staff in operating room. However, from our case, we have learned that intraoperative aspirator, protective clothing, N95 mask, and face shield can provide sufficient protection to our medical staff in the surgery room. What Patel et al[3] claimed in their work might provoke unnecessary anxiety toward endonasal endoscopic procedures based on an anecdotal statement.

In sum, as for medical staff, proper protective measures including N95 masks, face shield, protective clothing, and reduced contact with infected patients are necessary. No convincing evidence exists to show that there is an increased possibility of infection from the endoscopic transsphenoidal surgery under the above protective measures. At this emerging COVID-19 situation and for patients' safety, our advice is to avoid selective endoscopic transsphenoidal surgery unless in an emergency case, in which situation level-3 protection is definitely needed and a negative pressure operating room is recommended.

Disclosures

The retrospective survey in the letter was supported by the National Natural Science Foundation of China (grant 81272778 and 81974390 to Dr X. Jiang) and the Fundamental Research Funds for the Central Universities (grant 2020kfyXGYJ010 to Dr X. Jiang). The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Huang X, et al. Neurosurgery. 2020; 87:E160–161

15 April 2020

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Social media and rapid on-line publications…

17 April 2020

CASE REPORT

A COVID-19 Patient Who Underwent Endonasal Endoscopic Pituitary Adenoma Resection: A Case Report

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Received, April 1, 2020.
Accepted, April 1, 2020.
Published Online, April 17, 2020.

BACKGROUND AND IMPORTANCE: A pituitary adenoma patient who underwent surgery in our department was diagnosed with COVID-19 and 14 medical staff were confirmed infected later. This case has been cited several times but without accuracy or entirety, we feel obligated to report it and share our thoughts on the epidemic among medical staff and performing endonasal endoscopic surgery during COVID-19 pandemic.
CLINICAL PRESENTATION: The patient developed a fever 3 d post endonasal endoscopic surgery during which cerebrospinal leak occurred, and was confirmed with SARS-CoV-2 infection later. Several medical staff outside the operating room were diagnosed with COVID-19, while the ones who participated in the surgery were not.
CONCLUSION: The deceptive nature of COVID-19 results from its most frequent onset symptom, fever, a cliché in neurosurgery, which makes it hard for surgeons to differentiate. The COVID-19 epidemic among medical staff in our department was deemed as postoperative rather than intraoperative transmission, and attributed to not applying sufficient personal airway protection. Proper personal protective equipment and social distancing between medical staff contributed to limiting epidemic since the initial outbreak. Emergency endonasal endoscopic surgeries are feasible since COVID-19 is still supposed to be containable when the surgeries are performed in negative pressure operating rooms with personal protective equipment and the patients are kept under quarantine postoperatively. However, we do not encourage elective surgeries during this pandemic, which might put patients in conditions vulnerable to COVID-19.

KEY WORDS: Adenoma, COVID-19, Case report, Endonasal, Endoscopic

Neurosurgery 87:E140–E146, 2020 DOI:10.1093/neuros/nyaa147 www.neurosurgery-online.com

BACKGROUND AND IMPORTANCE

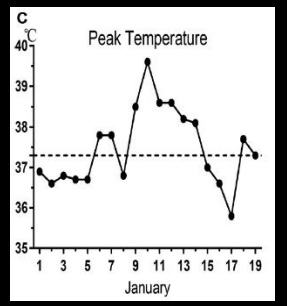
Since late December 2019, the COVID-19 outbreak has been causing concerns in the medical community and WHO characterized it as a pandemic on March 11th, 2020.[1] Wuhan used to be the epic center of the outbreak, a pituitary adenoma patient was the first diagnosed COVID-19 case in our department and 14 medical staff were confirmed infected later, and this specific case has been cited several times but without accuracy or entirety,[2,3] misinformation could lead to unnecessary psychological burden upon medical service providers. With this ongoing pandemic, we feel obligated to report it and share our thoughts and precautions to limit the epidemic among our medical staff.

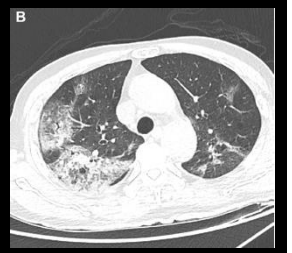
ABBREVIATIONS: CSF, cerebrospinal fluid; **FT3,** free triiodothyronine; **TSH,** thyroid-stimulating hormone; **WBC,** white blood cell count

CLINICAL PRESENTATION

Patient Information

A 70-yr-old male patient with a 2-mo history of visual impairment was admitted and then diagnosed with pituitary adenoma in late December 2019. His past medical history was significant for hypertension, diabetes, and heart attack, and medications included perindopril, metformin hydrochloride, atorvastatin, acarbose, and amlodipine. He had a family history of hypertension and denied direct or indirect contact with COVID-2019 patients or visiting Huanan Seafood Market in last 2 wk. Physical exam revealed bitemporal hemianopsia.





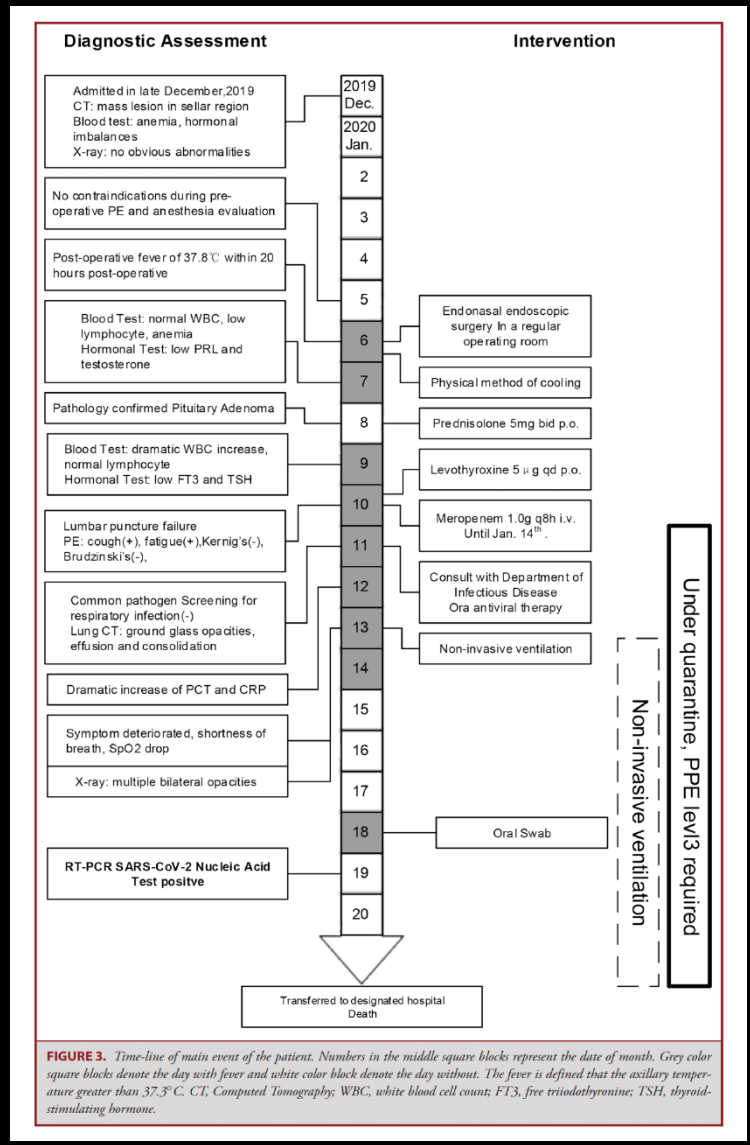


FIGURE 3. *Time-line of main event of the patient. Numbers in the middle square blocks represent the date of month. Grey color square blocks denote the day with fever and white color block denote the day without. The fever is defined that the axillary temperature greater than 37.3° C. CT, Computed Tomography; WBC, white blood cell count; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone.*

Zhu W, et al. Neurosurgery. 2020; 87:E140–146

Social media and rapid on-line publications…

17 April 2020

In Reply: Precautions for Endoscopic Transnasal Skull Base Surgery During the COVID-19 Pandemic

To the Editor:

COVID-19 has been spreading all over the world over the past 2 mo.[1] Owing to the striking increase of COVID-19 cases, the safety of medical workers is a concern.[2] Because the virus exists in all parts of the respiratory tract, there is a heated discussion on the timing of surgical treatment of respiratory diseases, especially the safety assessment of endoscopic transsphenoidal surgery in the department of neurosurgery.

Recently, Patel et al[3] submitted an article titled "Precautions for Endoscopic Transnasal Skull Base Surgery During the COVID-19 Pandemic" to remind the neurosurgeon and otolaryngologist to pay attention to the extended endoscopic skull base surgery of patients with COVID-19. In the article, Patel et al[3] cited the co-occurrence of 14 COVID-19 infected medical workers and a COVID-19 affected patient with pituitary adenoma who underwent endoscopic transsphenoidal surgery in our department, and stated the safety issue about the transsphenoidal surgery in this emerging COVID-19 situation. However, what was described does not accord with the facts.

The first argument is about the sentence "multiple members (>14 by report) of the patient care team, both within and outside of the operating room, became infected from what became recognized as human-to-human transmission of COVID-19". It is not accurate. At the early stage of the COVID-19 outbreak, we had 1 patient who underwent endoscopic transsphenoidal surgery on January 6, 2020 and was diagnosed with COVID-19 13 d later. Among the infected medical workers, 10 nurses and 4 neurosurgeons were diagnosed and only 4 nurses contacted the COVID-19 patient directly.

The second problem is that the authors[3] believed that all the medical workers who participated in the surgery were infected, especially from the experience of the second case that the author cited, for which we have no exact information in Wuhan neurosurgery medical system. However, according to our retrospective survey on our case, none of medical staff who participated in surgery were diagnosed with COVID-19 until March 31, 2020. Today, all the infected medical staff have recovered. More importantly, the medical workers diagnosed with COVID-19 in our department later were the staff who were outside the operation room. As for the infected neurosurgeon in our department, it's conceivable to be deemed as postoperative transmission rather than intraoperative transmission.

Finally, the opinion that the authors[3] delivered should be carefully assessed. The reason why the neurosurgeon and otolaryngologist were infected needs more data to illustrate. According to the whole infection event that we experienced, we have some facts and experiences to share with the medical community.

The reason why the infection event happened in our department at the early stage is due to little knowledge about COVID-19 and insufficient protective measures. Besides, the frequently interaction between medical workers in our department promoted transmission. Thus, accumulating information about the COVID-19 should be elucidated and reducing contact between people is a necessary means to prevent the spread of the virus.

In this infection event, more nurses were infected than surgeons, because nurses and patients are in direct contact, such as in daily medical care. So, compared to droplet transmission, contact transmission may be an important factor of transmission in medical workers which more likely we ignored at the early stage. Therefore, it is very important to wash hands and clean the surface of objects in wards and living areas. What's more, it is vital to make sure that once COVID-19 patients are confirmed, strict isolation measures must be taken as soon as possible.

As for the transsphenoidal surgery, Patel et al[3] believe that aerosol droplets coming from the endonasal surgery will increase the possibility of infection of medical staff in operating room. However, from our case, we have learned that intraoperative aspirator, protective clothing, N95 mask, and face shield can provide sufficient protection to our medical staff in the surgery room. What Patel et al[3] claimed in their work might provoke unnecessary anxiety toward endonasal endoscopic procedures based on an anecdotal statement.

In sum, as for medical staff, proper protective measures including N95 masks, face shield, protective clothing, and reduced contact with infected patients are necessary. No convincing evidence exists to show that there is an increased possibility of infection from the endoscopic transsphenoidal surgery under the above protective measures. At this emerging COVID-19 situation and for patients' safety, our advice is to avoid selective endoscopic transsphenoidal surgery unless in an emergency case, in which situation level-3 protection is definitely needed and a negative pressure operating room is recommended.

Disclosures

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Huang X, et al. Neurosurgery. 2020; 87:E160–161

23 April 2020

In Reply: Precautions for Endoscopic Transnasal Skull Base Surgery During the COVID-19 Pandemic

To the Editor:

Since the initial conception of our original letter to the editor,[1] the COVID-19 pandemic has unfortunately progressed to infect over 900 000 individuals resulting in over 45 000 deaths,[2] and is growing exponentially. Well-documented analysis has traced the travel of infected individuals from Wuhan, China, to New York, Milan, Tehran, and Madrid, cities in countries that in the last week have seen infection levels approach, if not exceed, levels at the initial epicenter in China.[3] Indeed, over half of all the world's documented infections are in Europe (450 000), and the United States is the country most plagued with over 200 000 cases.[2]

It was with that concern in mind that, when colleagues from China alerted us to the potential spread of COVID-19 to operating room staff, and with increasing reports of significant morbidity and mortality among otolaryngologists in several countries, we were motivated to rapidly share our concerns with the surgical community. The primary purpose of our Letter,[1] as the title suggests, was to alert the international readership of *Neurosurgery* that precautions for endoscopic transnasal skull base surgery during the COVID-19 pandemic were warranted. If our Letter[1] potentially prevented *one* infection, we would feel we have succeeded in our primary purpose.

The Wuhan group (Huang et al[4]), in their recent reply, raised an issue with our report that suggested the likelihood of intraoperative transmission. They confirmed that 14 individuals in their hospital, involved with the care of a COVID-19 patient undergoing transnasal surgery, indeed became infected, but raised the possibility that the infections were from direct contact outside the operating room and not from aerosolization of viral particles in the operating room. We thank them for their response and welcome their report. We acknowledge the difficulties in dealing with the earliest stages of the outbreak in Wuhan, and the controversy and/or challenges regarding its initial management.

Despite the absence of direct knowledge by the authors of the Reply Letter,[4] we did confirm that the second case of COVID-19 transmission from a patient who underwent emergent transnasal surgery for pituitary apoplexy, as documented in our report,[1] did occur at a different hospital in Wuhan, where providers in the operating room became infected despite the use of N95 personal protective equipment (PPE). Interestingly, the anesthesiologist in that case, who wore a powered air-purifying respirator (PAPR), was not infected. As we acknowledged in our Letter,[1] anecdotes and personal communications alone cannot provide the definitive evidence we need to make the best decisions regarding PPE in these cases. However, we feel it is unwise to ignore the evidence we do have: that viral load is high within the nasal cavity, that when performing endoscopic surgery we are working within and through that corridor, and that surgical maneuvers can aerosolize mucus particles along with any virus therein.

The concerns for potential spread during endonasal surgery in a COVID-19 patient remain high, and our recommendations for preoperative COVID-19 testing and use of PPE are strong. While we agree there is no hard data at this point proving that endonasal surgery in COVID-19 patients can cause widespread infection of operating room personnel, we feel that until further evidence becomes available the recommended precautions should remain in place: COVID-19 testing should be performed when possible, PPE should be employed for all endoscopic cases and for all involved personnel, surgery should be delayed when possible, consideration should be given to transcranial approaches for certain locations where possible, and PAPR use should be encouraged in the rare occurrence of a symptomatic COVID-19-positive patient needing emergent endonasal surgery.

We look forward with optimism towards the future of endonasal surgery, as COVID-19 testing becomes more rapid and widely available, which should help to inform our understanding of the immune response and immunity of both patients and providers. Similarly, worldwide efforts to control the pandemic, as demonstrated in China and South Korea, among others, will hopefully reduce the incidence of this disease in health care providers and in our potential patients.

We applaud the efforts of all physicians and surgeons serving in Wuhan and other corners of the globe, without whom the toll from this virus would have undoubtedly been much greater. We thank the authors for their response to our Letter, as we always welcome open scientific discourse and any information that can be shared globally regarding COVID-19-related cases in order to best protect our hospital teams, our patients, and ourselves.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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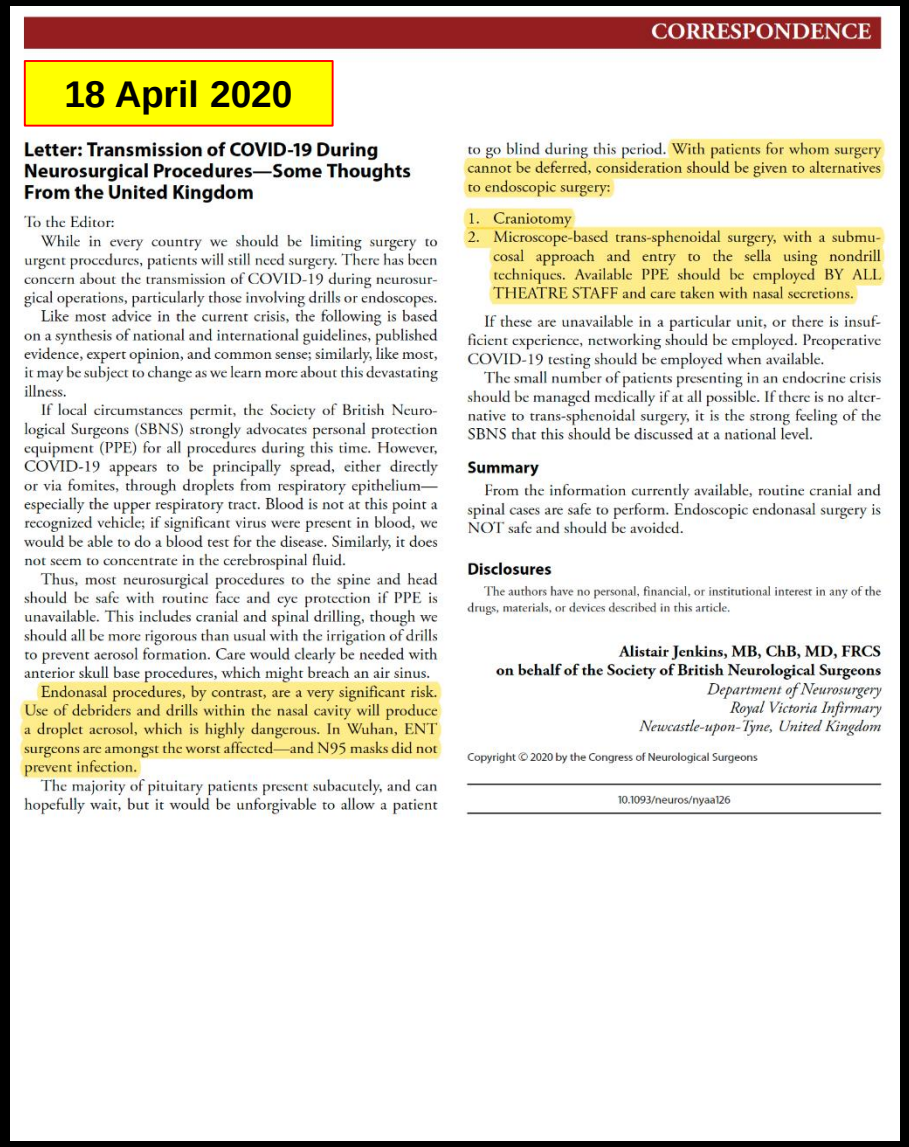
Patel ZM, et al. Neurosurgery. 2020. 87:E162–163

Social media and rapid on-line publications…



CORRESPONDENCE

18 April 2020

Letter: Transmission of COVID-19 During Neurosurgical Procedures—Some Thoughts From the United Kingdom

To the Editor:

While in every country we should be limiting surgery to urgent procedures, patients will still need surgery. There has been concern about the transmission of COVID-19 during neurosurgical operations, particularly those involving drills or endoscopes.

Like most advice in the current crisis, the following is based on a synthesis of national and international guidelines, published evidence, expert opinion, and common sense; similarly, like most, it may be subject to change as we learn more about this devastating illness.

If local circumstances permit, the Society of British Neurological Surgeons (SBNS) strongly advocates personal protection equipment (PPE) for all procedures during this time. However, COVID-19 appears to be principally spread, either directly or via fomites, through droplets from respiratory epithelium—especially the upper respiratory tract. Blood is not at this point a recognized vehicle; if significant virus were present in blood, we would be able to do a blood test for the disease. Similarly, it does not seem to concentrate in the cerebrospinal fluid.

Thus, most neurosurgical procedures to the spine and head should be safe with routine face and eye protection if PPE is unavailable. This includes cranial and spinal drilling, though we should all be more rigorous than usual with the irrigation of drills to prevent aerosol formation. Care would clearly be needed with anterior skull base procedures, which might breach an air sinus.

Endonasal procedures, by contrast, are a very significant risk. Use of debriders and drills within the nasal cavity will produce a droplet aerosol, which is highly dangerous. In Wuhan, ENT surgeons are amongst the worst affected—and N95 masks did not prevent infection.

The majority of pituitary patients present subacutely, and can hopefully wait, but it would be unforgivable to allow a patient to go blind during this period. With patients for whom surgery cannot be deferred, consideration should be given to alternatives to endoscopic surgery:

1. Craniotomy
2. Microscope-based trans-sphenoidal surgery, with a submucosal approach and entry to the sella using nondrill techniques. Available PPE should be employed BY ALL THEATRE STAFF and care taken with nasal secretions.

If these are unavailable in a particular unit, or there is insufficient experience, networking should be employed. Preoperative COVID-19 testing should be employed when available.

The small number of patients presenting in an endocrine crisis should be managed medically if at all possible. If there is no alternative to trans-sphenoidal surgery, it is the strong feeling of the SBNS that this should be discussed at a national level.

Summary

From the information currently available, routine cranial and spinal cases are safe to perform. Endoscopic endonasal surgery is NOT safe and should be avoided.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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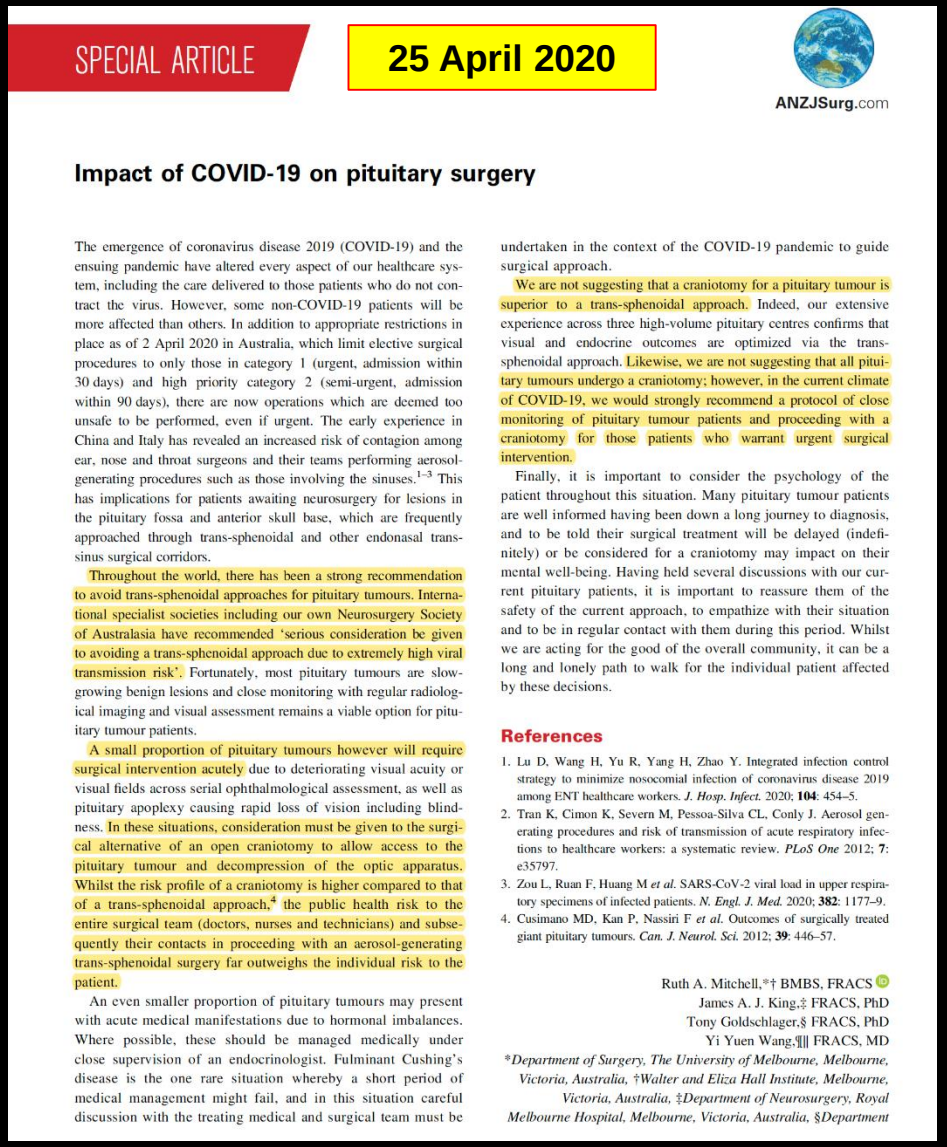
10.1093/neuros/nyaa126

Jenkins A. Neurosurgery. 2020; 87:E68



SPECIAL ARTICLE

25 April 2020

ANZJSurg.com

Impact of COVID-19 on pituitary surgery

The emergence of coronavirus disease 2019 (COVID-19) and the ensuing pandemic have altered every aspect of our healthcare system, including the care delivered to those patients who do not contract the virus. However, some non-COVID-19 patients will be more affected than others. In addition to appropriate restrictions in place as of 2 April 2020 in Australia, which limit elective surgical procedures to only those in category 1 (urgent, admission within 30 days) and high priority category 2 (semi-urgent, admission within 90 days), there are now operations which are deemed too unsafe to be performed, even if urgent. The early experience in China and Italy has revealed an increased risk of contagion among ear, nose and throat surgeons and their teams performing aerosol-generating procedures such as those involving the sinuses.[1–3] This has implications for patients awaiting neurosurgery for lesions in the pituitary fossa and anterior skull base, which are frequently approached through trans-sphenoidal and other endonasal transsinus surgical corridors.

Throughout the world, there has been a strong recommendation to avoid trans-sphenoidal approaches for pituitary tumours. International specialist societies including our own Neurosurgery Society of Australasia have recommended 'serious consideration be given to avoiding a trans-sphenoidal approach due to extremely high viral transmission risk'. Fortunately, most pituitary tumours are slow-growing benign lesions and close monitoring with regular radiological imaging and visual assessment remains a viable option for pituitary tumour patients.

A small proportion of pituitary tumours however will require surgical intervention acutely due to deteriorating visual acuity or visual fields across serial ophthalmological assessment, as well as pituitary apoplexy causing rapid loss of vision including blindness. In these situations, consideration must be given to the surgical alternative of an open craniotomy to allow access to the pituitary tumour and decompression of the optic apparatus. Whilst the risk profile of a craniotomy is higher compared to that of a trans-sphenoidal approach,[4] the public health risk to the entire surgical team (doctors, nurses and technicians) and subsequently their contacts in proceeding with an aerosol-generating trans-sphenoidal surgery far outweighs the individual risk to the patient.

An even smaller proportion of pituitary tumours may present with acute medical manifestations due to hormonal imbalances. Where possible, these should be managed medically under close supervision of an endocrinologist. Fulminant Cushing's disease is the one rare situation whereby a short period of medical management might fail, and in this situation careful discussion with the treating medical and surgical team must be undertaken in the context of the COVID-19 pandemic to guide surgical approach.

We are not suggesting that a craniotomy for a pituitary tumour is superior to a trans-sphenoidal approach. Indeed, our extensive experience across three high-volume pituitary centres confirms that visual and endocrine outcomes are optimized via the trans-sphenoidal approach. Likewise, we are not suggesting that all pituitary tumours undergo a craniotomy; however, in the current climate of COVID-19, we would strongly recommend a protocol of close monitoring of pituitary tumour patients and proceeding with a craniotomy for those patients who warrant urgent surgical intervention.

Finally, it is important to consider the psychology of the patient throughout this situation. Many pituitary tumour patients are well informed having been down a long journey to diagnosis, and to be told their surgical treatment will be delayed (indefinitely) or be considered for a craniotomy may impact on their mental well-being. Having held several discussions with our current pituitary patients, it is important to reassure them of the safety of the current approach, to empathize with their situation and to be in regular contact with them during this period. Whilst we are acting for the good of the overall community, it can be a long and lonely path to walk for the individual patient affected by these decisions.

References

1. Lu D, Wang H, Yu R, Yang H, Zhao Y. Integrated infection control strategy to minimize nosocomial infection of coronavirus disease 2019 among ENT healthcare workers. *J. Hosp. Infect.* 2020; **104**: 454–5.
2. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012; **7**: e35797.
3. Zou L, Ruan F, Huang M *et al.* SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N. Engl. J. Med.* 2020; **382**: 1177–9.
4. Cusimano MD, Kan P, Nassiri F *et al.* Outcomes of surgically treated giant pituitary tumours. *Can. J. Neurol. Sci.* 2012; **39**: 446–57.

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Mitchell RA, et al. ANZ J Surg. 2020; 90:E963–964

Cambridge UK approach (March/April 2020)

1. Patients who require expedited surgery for a pituitary or skull base lesion due to progressive neurological, visual symptoms or potential malignancy should still receive urgent treatment[1]

2. Where possible, standard of care should be offered (including endoscopic transnasal surgery for pituitary tumours)[1]

3. Development of a risk mitigation strategy to address the concerns raised on social media and in the emerging literature[1]

4. Multidisciplinary team ownership: neurosurgery, otolaryngology, anaesthesia, nursing (theatre and ward teams), infectious diseases & endocrinology

1. Kolias A, et al. Acta Neurochir (Wien). 2020; 162:1509–1511

Risk mitigation for pituitary surgery during COVID-19 pandemic

Pre-operative phase

Screen for COVID-19 symptoms one week prior to surgery
- persistent new cough, fever etc. – affecting patient or member of their household

In the absence of any symptoms, ask patient to self-isolate until operation

Perform nasopharyngeal swabs on two occasions prior to surgery
- day 4–5 pre-operatively and day 2 pre-operatively

If both swabs negative, admit on day of surgery
- re-screen for COVID-19 symptoms

Use 0.5% povidone-iodine (PVP-I)
- applied to skin and mucous membranes (as mouth wash)

Kolias A, et al. Acta Neurochir (Wien). 2020; 162:1509–1511

Risk mitigation for pituitary surgery during COVID-19 pandemic

Intra-operative phase

Follow hospital's COVID-19 protocol in each operating room
- green/amber/red zones

Full personal protective equipment (PPE) for all staff in amber & red zones
- full gown, gloves, FFP3 respirator, full face shield

Microdebriders and drills used with concurrent suction
- as per usual practice

0.5% povidone-iodine (PVP-I)
- applied to skin and mucous membranes (each nostril)

Avoidance of nasal packing

Intubation and extubation performed in the operating room

Kolias A, et al. Acta Neurochir (Wien). 2020; 162:1509–1511

Risk mitigation for pituitary surgery during COVID-19 pandemic

A safe approach to surgery for pituitary and skull base lesions during the COVID-19 pandemic

Angelos Kolias[1] · James Tysome[2] · Neil Donnelly[2] · Rishi Sharma[2] · Effrossyni Gkrania–Klotsas[3] · Karol Budohoski[1] · Silvia Karcheva[4] · Ram Adapa[4] · Indu Lawes[1] · Mark Gurnell[5] · Peter Hutchinson[1] · Manohar Bance[2] · Patrick Axon[2] · Thomas Santarius[1] · Richard J. Mannion[1]

57 healthcare workers – no staff sickness or cases of COVID-19 (mean follow-up 17 days; median 13 days)

Age group, gender	Indication for surgery	Approach used	Post-operative hospital stay; discharge destination	COVID-19 status; days of follow-up since operation
25–30 years old, male	Vestibular schwannoma (38 mm) with brainstem compression and ataxia	Translabyrinthine	3 days; usual residence	No symptoms; 29 days
30–35 years old, female	Vestibular schwannoma (40 mm) with brainstem compression and early hydrocephalus	Translabyrinthine	3 days; usual residence	No symptoms; 28 days
40–45 years old, male	Pituitary macroadenoma with compression of optic chiasm, reduced visual acuity, and bitemporal hemianopia	Endoscopic, transsphenoidal	5 days; usual residence	No symptoms; 27 days
56–60 years old, female	C2 tumor extending in spinal canal and prevertebral space (appearances suspicious for chordoma)	Transoral biopsy	1 day; usual residence	No symptoms; 19 days
50–55 years old, male	Pituitary macroadenoma with compression of optic chiasm and bitemporal superior quadrantanopia	Endoscopic, transsphenoidal	4 days; usual residence	No symptoms; 13 days
70–75 years old, male	Pituitary macroadenoma with compression of optic chiasm and bitemporal superior quadrantanopia	Endoscopic, transsphenoidal	2 days; usual residence	No symptoms; 13 days
70–75 years old, male	Olfactory neuroblastoma (Hyams grade 4 confirmed with biopsy)	Combined endoscopic endonasal and transcranial	Remains an inpatient for inpatient rehabilitation	Post-operative fever but swab negative; 12 days
50–55 years old, male	Pituitary macroadenoma with compression of optic chiasm and bitemporal superior quadrantanopia	Endoscopic, transsphenoidal	2 days; usual residence	No symptoms; 7 days
46–50 years old, female	Vestibular schwannoma (43 mm) with brainstem compression and early hydrocephalus	Translabyrinthine	3 days; usual residence	No symptoms; 5 days

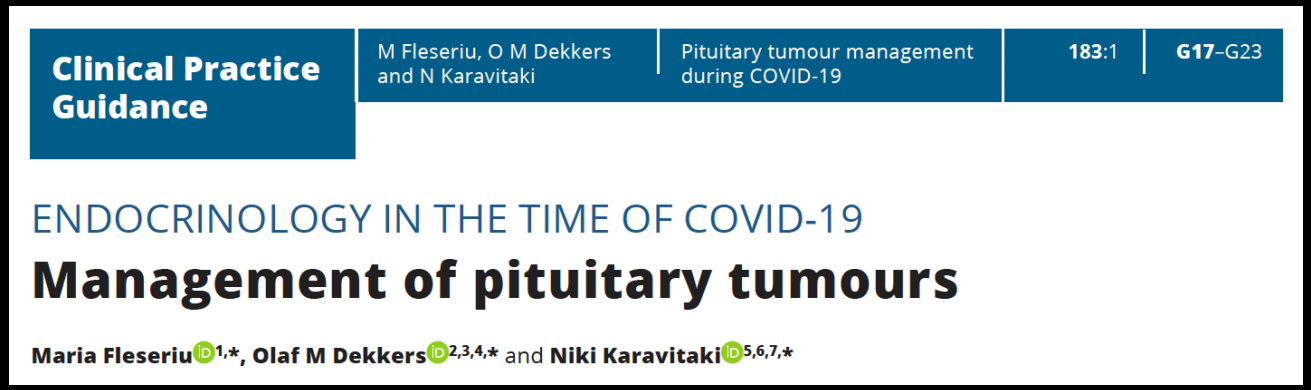
Kolias A, et al. Acta Neurochir (Wien). 2020; 162:1509–1511

World Federation of Neurosurgical Societies: https://www.wfns.org/newsletter/209

Management of pituitary tumours during COVID-19 pandemic

International guidance

05 May 2020



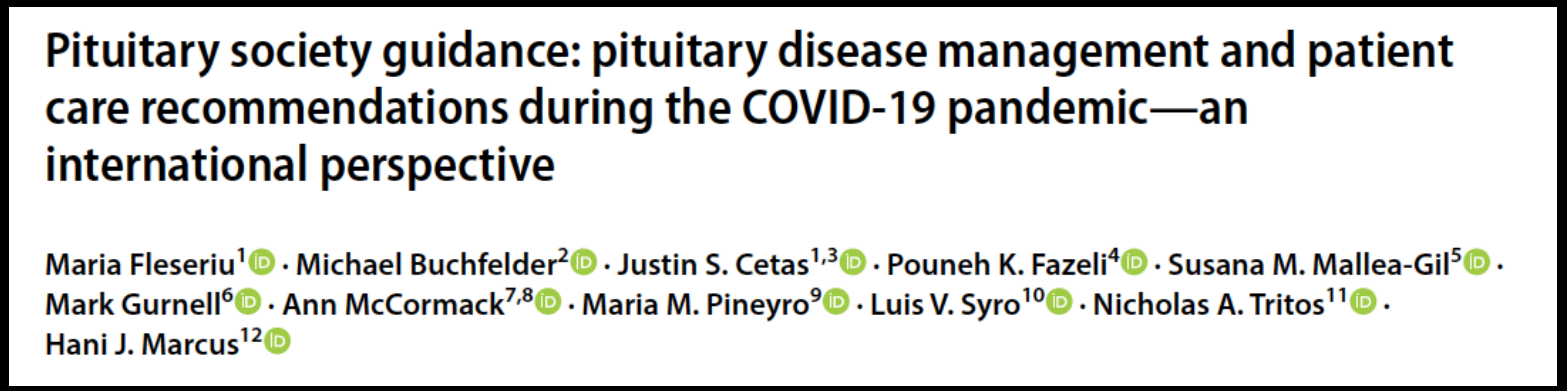
Clinical Practice Guidance | M Fleseriu, O M Dekkers and N Karavitaki | Pituitary tumour management during COVID-19 | **183**:1 | **G17**–G23

ENDOCRINOLOGY IN THE TIME OF COVID-19

Management of pituitary tumours

Maria Fleseriu[1,*], **Olaf M Dekkers**[2,3,4,*] and **Niki Karavitaki**[5,6,7,*]

18 June 2020



Pituitary society guidance: pituitary disease management and patient care recommendations during the COVID-19 pandemic—an international perspective

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Fleseriu M, et al. Eur J Endocrinol. 2020; 183:G17–23
Fleseriu M, et al. Pituitary. 2020; 23:327–337

Management of pituitary tumours during COVID-19 pandemic

International guidance

Transsphenoidal surgery in the COVID-19 pandemic era

- Based on very recent, but still anecdotal data, endonasal surgery (endoscopic or microscopic) for COVID-19 positive patients with pituitary tumours is considered a high-risk procedure (12). As a result of this, several neurosurgical groups across the world are currently undertaking only urgent surgeries and postponing elective surgeries.
- Testing for COVID-19 infection is strongly recommended 48 h prior to transsphenoidal surgery. If the results are positive, deferring surgery until infection is cleared needs to be considered. If this is not possible, appropriate personal protective equipment (PPE) for anyone in the operating theatre is recommended (12). Furthermore, given the possibility of false-negative results for COVID-19 testing, the surgical theatre team should still wear full PPE even in COVID-19 negative cases, as these surgical procedures are aerosol generating.

Table 1 Pituitary surgery challenges and recommendations during COVID-19 pandemic

Factor	Challenges	Recommendations
COVID-19	High prevalence of cases in the community during pandemic and risk of additional waves in the post-peak phase	Screening for cough, fever, and other symptoms and, if suspected, swab for testing *Consider* Isolation up to two weeks before surgery Paired swabs for testing and/or serological tests Chest X-ray and/or chest CT*
Patient	High risk of older patients with comorbid conditions contracting COVID-19; consider natural history of pituitary disease	Emergency surgery if pituitary apoplexy, acute severe visual loss or other evidence of significant mass effect, or if there is concern regarding malignant pathology *Consider* Surgery for patients with less acute, but progressive visual loss, functioning tumors with aggressive clinical features, and those with an unclear diagnosis
Surgeon	Risk of surgeon contracting COVID-19 from patient	In a patient with COVID-19 that requires emergent surgery that cannot be deferred, alternative transcranial approaches may be considered, drilling avoided, and full PPE is mandated *Consider* Full PPE in all cases
Institution	Diversion of resources to (non-pituitary) patients with COVID-19	Maintain flexibility for second wave

PPE personal protective equipment

*Depending on local guidance, chest CT is mandatory in some centers

TSS, transsphenoidal surgery

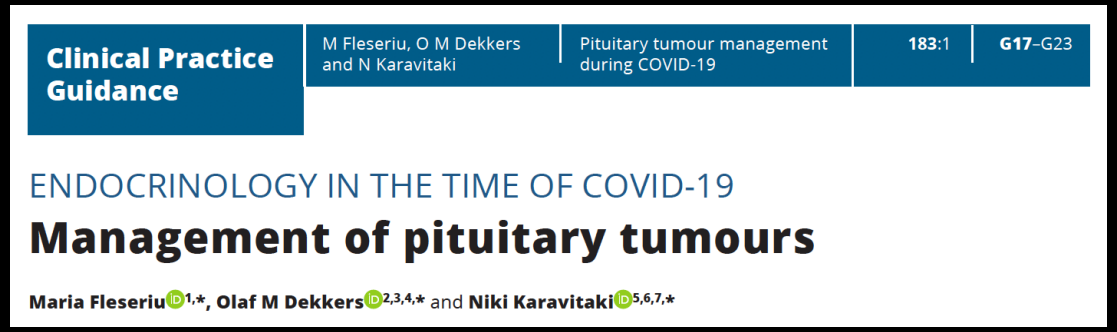
In most cases, TSS remains the safest, most effective, and most efficient approach to pituitary tumors. In a series

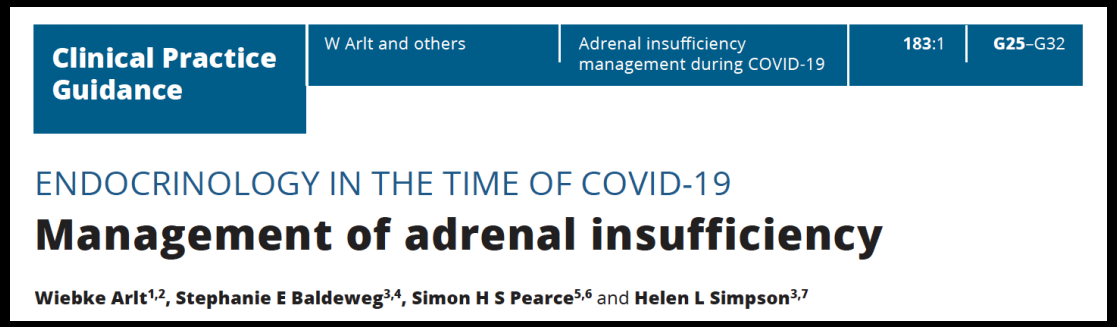
Fleseriu M, et al. Eur J Endocrinol. 2020; 183:G17–23

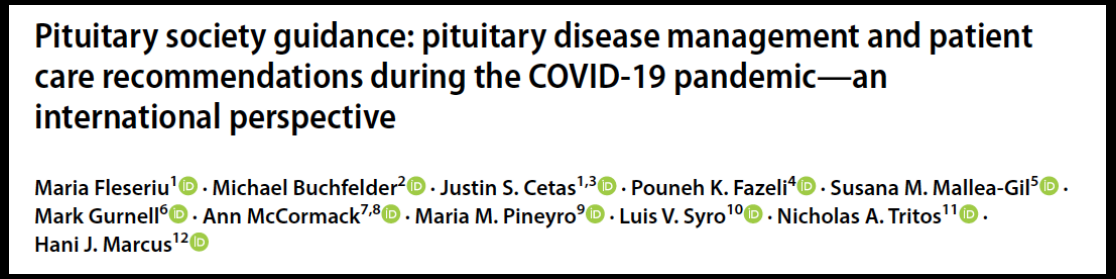
Fleseriu M, et al. Pituitary. 2020; 23:327–337

Hypopituitarism during COVID-19 pandemic

International guidance







Christ-Crain M, et al. Eur J Endocrinol. 2020; 183: G9–15

Fleseriu M, et al. Eur J Endocrinol. 2020; 183:G17–23

Arlt W, et al. Eur J Endocrinol. 2020; 183:G25–32

Fleseriu M, et al. Pituitary. 2020; 23:327–337

Caring for patients with hypopituitarism during COVID-19 pandemic

General principles

1. Minimise requirement for hospital attendance
2. Utilise telephone/virtual clinic reviews where possible
3. Provide clear guidance on management of endocrine replacement therapies (including in the event of developing COVID-19)
4. Ensure all pituitary patients have timely access to clinical advice/support

Diagnosis of hypopituitarism during COVID-19 pandemic

Choice of investigations:

HPA: 9am cortisol (± 250 mcg cosyntropin test *vs empirical treatment*)

HPT: free T4 & TSH

HPG: *when indicated* LH/FSH & testosterone or estradiol (± prolactin)

HPS: *defer until dynamic testing available*

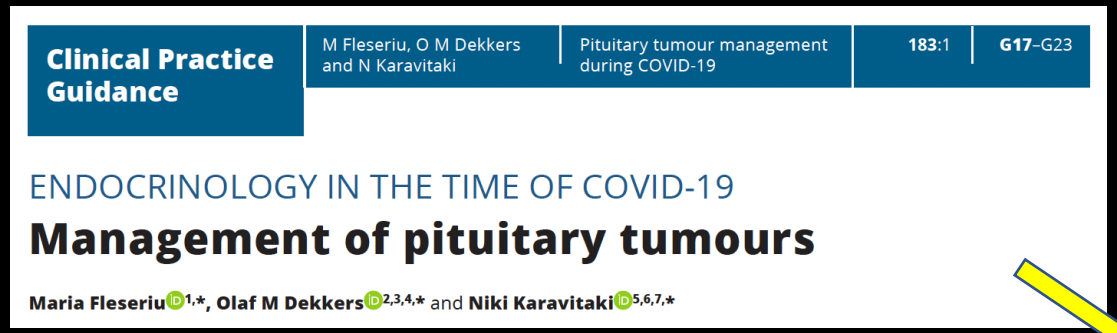
DI: *consider pre-test probability then* serum sodium & osmolality

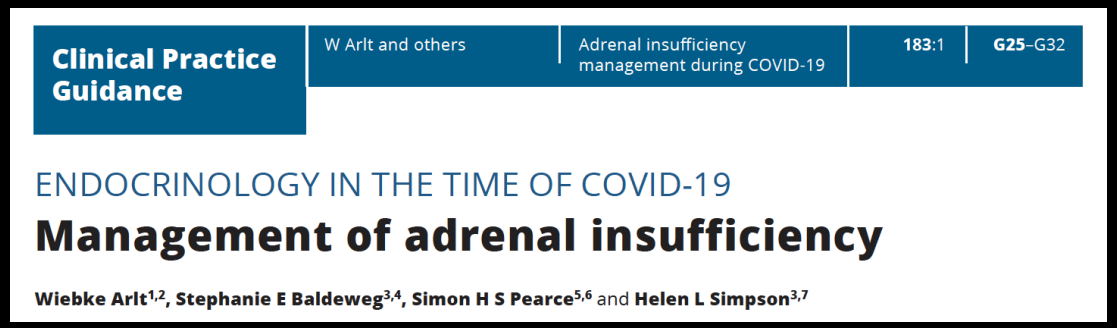
DI, diabetes insipidus; FSH, follicle stimulating hormone; LH, luteinising hormone; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; HPS, hypothalamic–pituitary–somatotropic; HPT, hypothalamic-pituitary-thyroid; T4, thyroxine; TSH, thyroid stimulating hormone

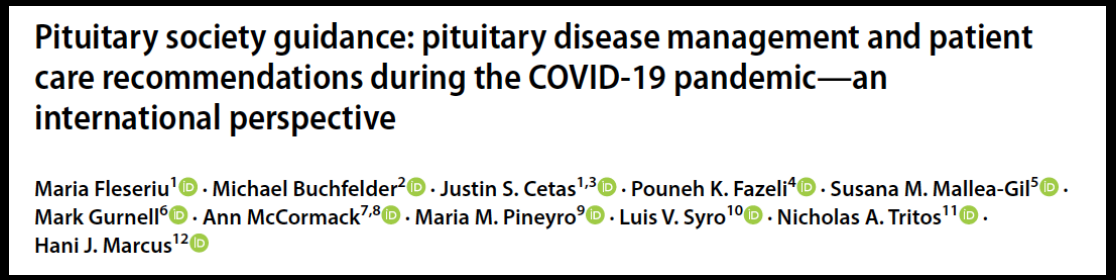
Fleseriu M, et al. Pituitary. 2020; 23:327–337

Management of hypopituitarism during COVID-19 pandemic

Management:







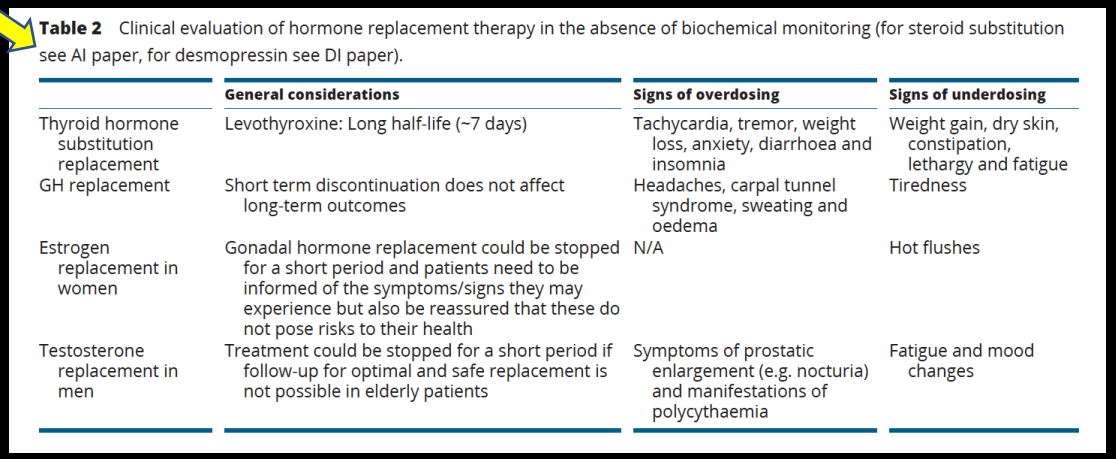


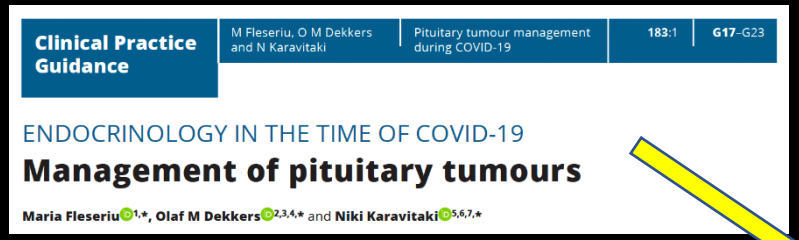
Table 2 Clinical evaluation of hormone replacement therapy in the absence of biochemical monitoring (for steroid substitution see AI paper, for desmopressin see DI paper).

	General considerations	Signs of overdosing	Signs of underdosing
Thyroid hormone substitution replacement	Levothyroxine: Long half-life (~7 days)	Tachycardia, tremor, weight loss, anxiety, diarrhoea and insomnia	Weight gain, dry skin, constipation, lethargy and fatigue
GH replacement	Short term discontinuation does not affect long-term outcomes	Headaches, carpal tunnel syndrome, sweating and oedema	Tiredness
Estrogen replacement in women	Gonadal hormone replacement could be stopped for a short period and patients need to be informed of the symptoms/signs they may experience but also be reassured that these do not pose risks to their health	N/A	Hot flushes
Testosterone replacement in men	Treatment could be stopped for a short period if follow-up for optimal and safe replacement is not possible in elderly patients	Symptoms of prostatic enlargement (e.g. nocturia) and manifestations of polycythaemia	Fatigue and mood changes

Christ-Crain M, et al. Eur J Endocrinol. 2020; 183: G9–15
Fleseriu M, et al. Eur J Endocrinol. 2020; 183:G17–23
Arlt W, et al. Eur J Endocrinol. 2020; 183:G25–32
Fleseriu M, et al. Pituitary. 2020; 23:327–337

Management of hypopituitarism during COVID-19 pandemic

Management:



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Fleseriu M, et al. Eur J Endocrinol. 2020; 183:G17–23

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NHS University Hospitals Birmingham NHS Foundation Trust

Dilemmas in Pituitary Disease Management during the COVID-19 Era

ACROMEGALY

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Birmingham Health Partners
UK

Pituitary Disease Webinar, 30th July 2020

Disclosures

- Grants/consultancy: Ipsen, Novartis and Pfizer

ENDOCRINOLOGY IN THE TIME OF COVID-19

Management of pituitary tumours

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*(M Fleseriu, O M Dekkers and N Karavitaki contributed equally to this work)

This manuscript is part of a commissioned series of urgent clinical guidance documents on the management of endocrine conditions in the time of COVID-19. This clinical guidance document underwent expedited open peer review by Cesar Boguszewski (Federal University of Parana, Curitiba, Brazil), Jens-Otto Jorgensen (Aarhus University Hospital, Denmark), Dominique Maiter (Université catholique de Louvain and Cliniques Universitaires Saint-Luc, Brussels, Belgium), and Ken Ho (University of New South Wales and St. Vincent's Hospital, Sydney, Australia)

European Journal of Endocrinology (2020) **183**, G17–G23

Pituitary (2020) 23:327–337
https://doi.org/10.1007/s11102-020-01059-7

Check for updates

Pituitary society guidance: pituitary disease management and patient care recommendations during the COVID-19 pandemic—an international perspective

Maria Fleseriu[1] · Michael Buchfelder[2] · Justin S. Cetas[1,3] · Pouneh K. Fazeli[4] · Susana M. Mallea-Gil[5] · Mark Gurnell[6] · Ann McCormack[7,8] · Maria M. Pineyro[9] · Luis V. Syro[10] · Nicholas A. Tritos[11] · Hani J. Marcus[12]

Acromegaly during COVID-19 era

- **Rapid expert consensus, not based on systematic review or meta-analysis**
- **Individual circumstances, local country and region particularities (viral load, COVID-19 burden and healthcare availabilities) need to be considered when devising care plan for each specific patient**

Eur J Endocrinol. 2020;183(1):G17-G23. *Pituitary.* 2020;23(4):327-337

Pre-COVID-19 pandemic

Diagnosis

1.1 We recommend measurement of IGF-1 levels in patients with typical clinical manifestations of acromegaly, especially those with acral and facial features. (1|⊕⊕⊕◯)

1.2 We suggest the measurement of IGF-1 in patients without the typical manifestations of acromegaly, but who have several of these associated conditions: sleep apnea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension. (2|⊕⊕◯◯)

IGF-1, insulin-like growth factor 1.

J Clin Endocrinol Metab. 2014;99(11):3933-3951

Pre-COVID-19 pandemic
Diagnosis

1.5 In patients with elevated or equivocal serum IGF-1 levels, we recommend confirmation of the diagnosis by finding lack of suppression of GH to < 1 μg/L following documented hyperglycemia during an oral glucose load. (1|⊕⊕⊕◯)

1.6 Following biochemical diagnosis of acromegaly, we recommend performing an imaging study to visualize

1.7 We suggest performing formal visual field testing when the tumor is found to abut the optic chiasm on an imaging study. (2|⊕⊕⊕◯)

GH, growth hormone; IGF-1, insulin-like growth factor 1.

J Clin Endocrinol Metab. 2014;99(11):3933-3951

During COVID-19 pandemic
Diagnosis

- **Operation of health care services reduced or limited**
- **Patients often reluctant to seek medical attention or to have face-to-face consultations out of fear of possible exposure to COVID-19**

VIRTUAL CLINIC APPOINTMENTS

TELEPHONE CONTACT

VIDEO LINK (SECURE INTERNET-BASED PLATFORM)

Eur J Endocrinol. 2020;183(1):G17-G23. *Pituitary.* 2020;23(4):327-337

During COVID-19 pandemic

Diagnosis

VIRTUAL CLINIC APPOINTMENT

- **Detailed history (particular emphasis on visual deterioration, acromegaly-related comorbidities)**
- **Limited physical examination (e.g. inspection of face, skin, extremities)**
- **Arrange hormonal tests (in satellite COVID-free sites, if possible)**
  - **IGF-1**
  - **OGTT (not necessary in <u>unequivocally high</u> IGF-1 and typical clinical picture)**

What if patient has IGF-I 1.5 x ULN ?

IGF-1, insulin-like growth factor 1; OGTT, oral glucose tolerance test; ULN, upper limit of normal.

Eur J Endocrinol. 2020;183(1):G17-G23. *Pituitary.* 2020;23(4):327-337

During COVID-19 pandemic
Diagnosis

- **After confirmation of diagnosis arrange:**
  - **Dedicated pituitary imaging (CT or MRI, in satellite COVID-free sites if possible)**
  - **Visual assessment (cranial nerves, VA, VFs if indicated clinically or from imaging appearances)**
  - **Remaining pituitary hormone profile combined with routine biochemistry (including metabolic profile)**

CT, computed tomography; MRI, magnetic resonance imaging; VA, visual acuity; VF, visual fields.

Personal views. *Eur J Endocrinol.* 2020;183(1):G17-G23. *Pituitary.* 2020;23(4):327-337

During COVID-19 pandemic
After diagnosis

VIRTUAL CLINIC APPOINTMENT

- **Discuss diagnosis and its implications**
- **Discuss diagnostic and management approach of possible acromegaly-related comorbidities and hypopituitarism (impact on COVID-19 infection prognosis)**
- **Agree on a safe/effective management and follow-up plan**
- **Alleviate patient's stress**

Eur J Endocrinol. 2020;183(1):G17-G23. *Pituitary.* 2020;23(4):327-337

During COVID-19 pandemic
After diagnosis

- **Approach to acromegaly-related comorbidities**
  - **Cardiovascular: aim for optimal control of hypertension (in collaboration with primary care), defer echocardiogram unless clinically indicated**
  - **Glucose metabolism: aim for optimal control of glucose abnormalities (in collaboration with primary care)**

Personal views. *Eur J Endocrinol.* 2020;183(1):G17-G23. *Pituitary.* 2020;23(4):327-337

During COVID-19 pandemic
After diagnosis

- **Approach to acromegaly-related comorbidities**
  - **OSA: screening by history and sleep questionnaire, defer polysomnography unless suspicion of severe OSA**
  - **Musculoskeletal (arthropathy, carpal tunnel syndrome, vertebral fractures): defer investigations, unless severe clinical indications**
  - **Colonoscopy: defer, unless severe clinical indications**

OSA, obstructive sleep apnea.

Pre-COVID-19 pandemic
Management

3.0 Goals of management

3.1 We suggest a biochemical target goal of an age-normalized serum IGF-1 value, which signifies control of acromegaly. (2|⊕⊕◯◯)

3.2 We suggest using a random GH < 1.0 μg/L as a therapeutic goal, as this correlates with control of acromegaly. (2|⊕◯◯◯)

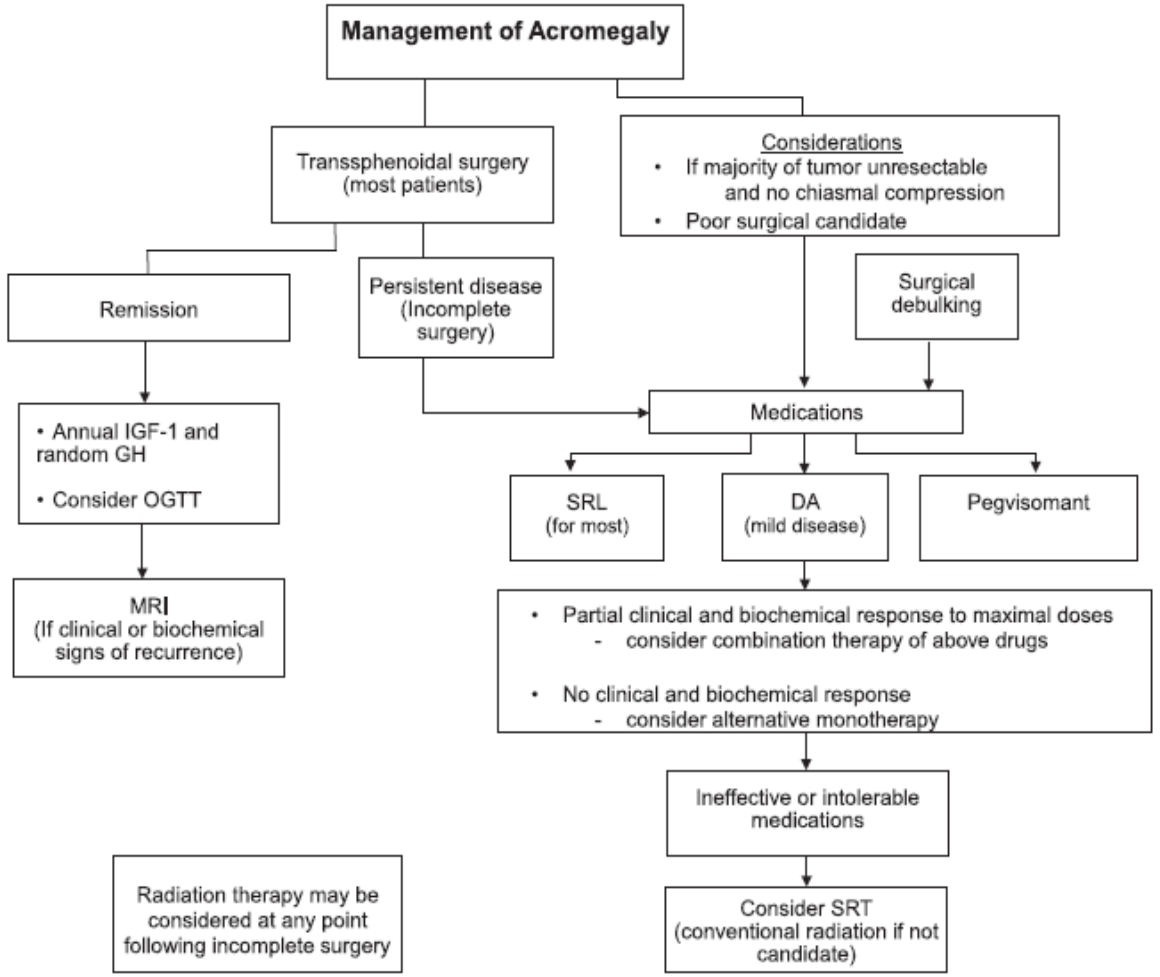


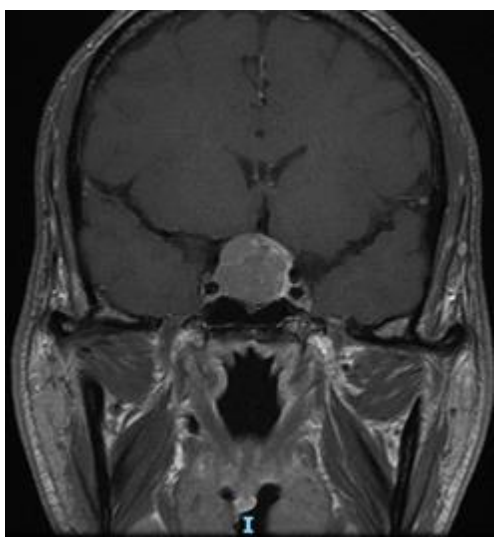
Figure 1. Treatment considerations in the approach to a patient with acromegaly. This approach refers to management of a patient wit pituitary adenoma. DA, dopamine agonist; OGTT, oral glucose tolerance test.

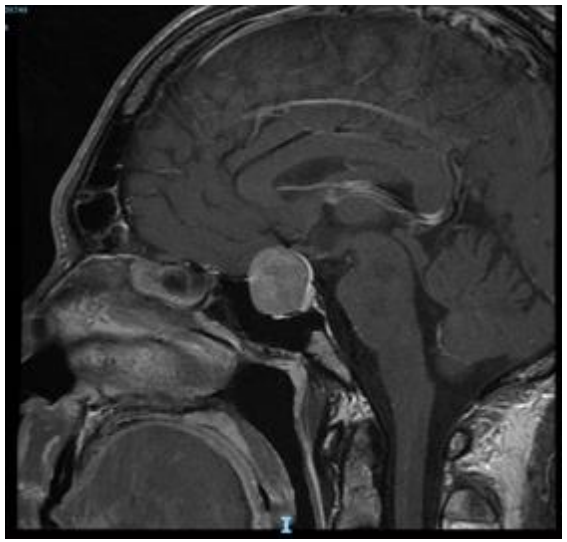
DA, dopamine agonist; GH, growth hormone; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; SRL, somatostatin receptor ligand; SRT, stereotactic radiation therapy.

J Clin Endocrinol Metab. 2014;99(11):3933-3951

During COVID-19 pandemic
Management

- **Case 1**
  - **Male, 48 years**
  - **Recent diagnosis of acromegaly, IGF-1 4xULN, no OGTT, PRL normal**
  - **Bitemporal hemianopia**
  - **Pituitary MRI**





IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; PRL, prolactin; ULN, upper limit of normal.

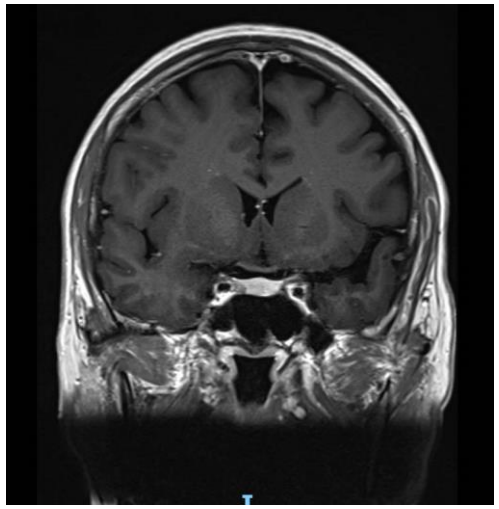
During COVID-19 pandemic
Management

- <u>Case 1</u>
  - First line treatment: Surgery

- INDICATIONS FOR SURGERY
  - Visual deterioration
  - Apoplexy with visual dysfunction (not improving or deteriorating)

During COVID-19 pandemic
Management

- **Case 2**
  - **Female, 38 years**
  - **Change in facial appearances consistent with acromegaly in the last 4 years, acral enlargement**
  - **Recent diagnosis of acromegaly, IGF-1 1.3xULN, no OGTT, PRL normal**
  - **No visual dysfunction**
  - **Pituitary MRI**



IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; PRL, prolactin; ULN, upper limit of normal.

During COVID-19 pandemic
Management

- **Case 2**
  - **Wait for further management at a later stage**

    OR

  - **Consider treatment with cabergoline**
    - **Virtual clinic appointment for monitoring and dose titration based on**
      - ✓ **clinical picture**
      - ✓ **adverse effects**
      - ✓ **IGF-I measurement (when safe to arrange)**

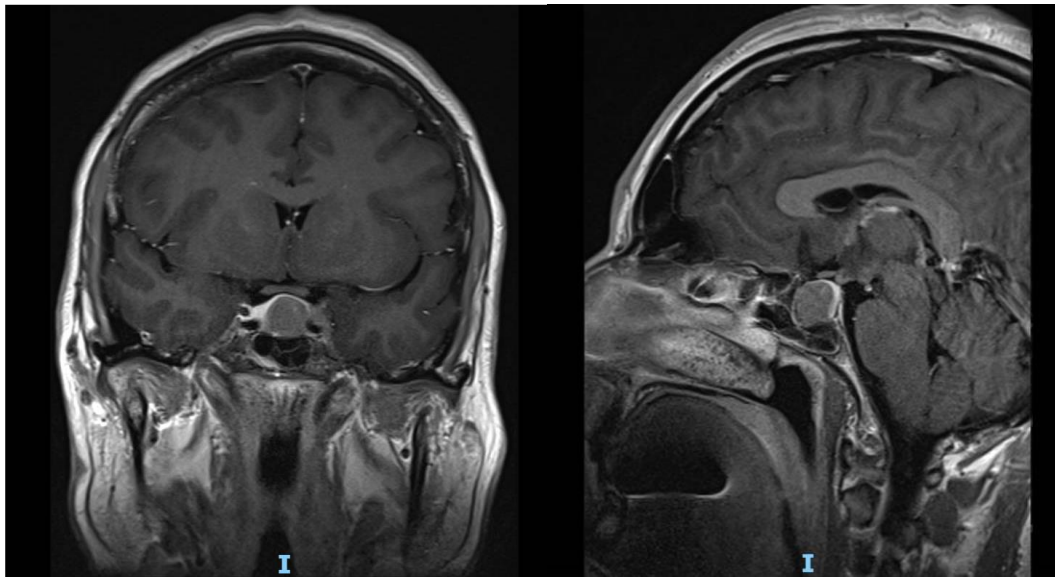
Normalisation in IGF-1 in 34% of cases

J Clin Endocrinol Metab. 2011 May;96(5):1327-35.

IGF-1, insulin-like growth factor 1.

During COVID-19 pandemic
Management

- **Case 3**
  - **Female, 42 years**
  - **Recent diagnosis of acromegaly, IGF-1 3xULN, no OGTT, PRL normal**
  - **No visual dysfunction**
  - **Pituitary MRI**



IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging;
OGTT, oral glucose tolerance test; PRL, prolactin; ULN, upper limit of normal.

During COVID-19 pandemic
Management

- <u>Case 3</u> - Individualized approach

- Medical treatment

Somatostatin analogue (SSA)
Octreotide 100-200 mcg tds *sc* *
Lanreotide 120 mg deep *sc* every 6-8 wks *
Octreotide LAR 30 mg *im* every 6-8 wks
*** self-injected**

Addition of cabergoline, if no response, depending on regulatory approval

Training of patients or family members on administration of injections by online visits or by video

Consider pegvisomant *sc* * with gradual dose titration in small tumours and normal liver function depending on country availability and regulatory approval
*** self-injected**

im, intramuscular; *sc*, subcutaneous; tds, three times a day.

During COVID-19 pandemic
Management

- **<u>Case 3</u> - Individualized approach**
  - **Virtual clinic appointment for monitoring, dose titration or amending regime based on**
    - ✓ **clinical picture**
    - ✓ **adverse effects**
    - ✓ **IGF-1 measurement (when safe to arrange)**

IGF-1, insulin-like growth factor 1.

During COVID-19 pandemic
Management

- **Patients on regular/routine monitoring**

Generally, treatment regimens should not be changed for a period of 6 months, unless there is a strong clinical suspicion of significant changes in the response to therapy or presence of adverse effects

A potential exception could be patients with acromegaly controlled on long-acting SRLs. In this group, an increase in their dose aiming to reduce the frequency of injections should be considered, as rates of adverse events seem to be similar.

Plans for radiotherapy during the COVID-19 pandemic need to be postponed for 6 months with review of further plans later.

Imaging for functioning pituitary tumours, well-controlled by medical treatment, is not advised as hormonal and tumour mass responses are only rarely discordant.

SRL, somatostatin receptor ligand.

Eur J Endocrinol. 2020;183(1):G17-G23

During COVID-19 pandemic

Management

- **Patients diagnosed with COVID-19 infection**

In patients with pituitary tumours diagnosed with COVID-19 infection, an urgent virtual clinic appointment is recommended, aiming to cover the implications of COVID-19 infection in the setting of cortisol deficiency, presence of various co-morbidities (e.g. obesity, hypertension, diabetes mellitus and cardiovascular diseases) and presence of adverse effects of medical treatments (e.g. gastrointestinal side effects, liver dysfunction related with medical treatment for acromegaly). In the last scenario, stopping or postponing the administration of the responsible drug is recommended.

Eur J Endocrinol. 2020;183(1):G17-G23

Acromegaly during COVID-19 era

What has changed? – Take home messages

- ✓ **Provision of care through virtual clinics – consider them as part of a "hybrid" model of care in the future?**
- ✓ **Simplify confirmation of diagnosis**
- ✓ **Emphasize tight control of comorbidities with potentially negative impact on COVID-19 infection**
- ✓ **Individualize approach to other acromegaly-related comorbidities**

Acromegaly during COVID-19 era

What has changed? – Take home messages

- ✓ If visual deterioration, 1st line treatment is surgery
- ✓ In other cases, medical treatment with individualized approach and aim to minimize face-to-face contact with health care professionals and services…this may change if issues on safety of surgery alleviate
- ✓ In cases controlled with long-acting somatostatin analogue, consider increasing dose aiming to reduce the frequency of injections
- ✓ Close collaboration with patient support groups to disseminate reliable information/guidance and to provide reassurance

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Acromegaly during COVID-19 era

Lessons to be learnt

Exploit valuable experience in acromegaly diagnosis, management and follow-up gained during these challenging times

Thank you!

Garvan Institute of Medical Research

Cushing's Disease

during the COVID-19 era

A/Professor Ann McCormack

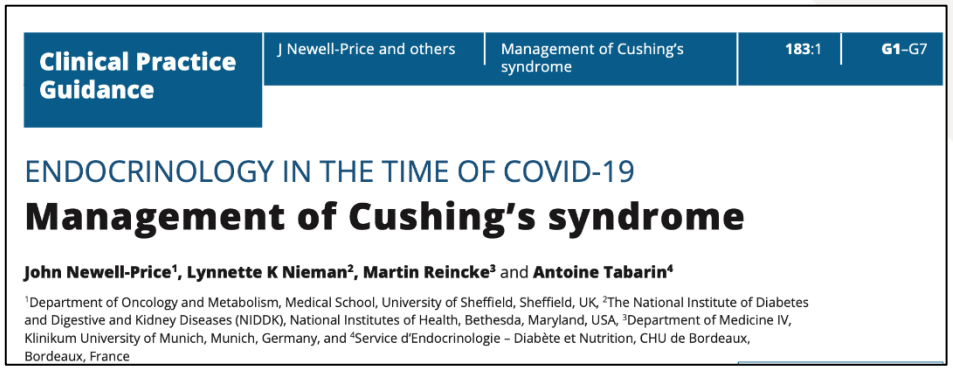
UNSW SYDNEY Australia's Global University

ST VINCENT'S HEALTH AUSTRALIA

Disclosures

- Grants/consultancy: Ipsen, Novartis, Pfizer

Management Principles



Clinical Practice Guidance | J Newell-Price and others | Management of Cushing's syndrome | 183:1 | G1–G7

ENDOCRINOLOGY IN THE TIME OF COVID-19

Management of Cushing's syndrome

John Newell-Price[1], Lynnette K Nieman[2], Martin Reincke[3] and Antoine Tabarin[4]

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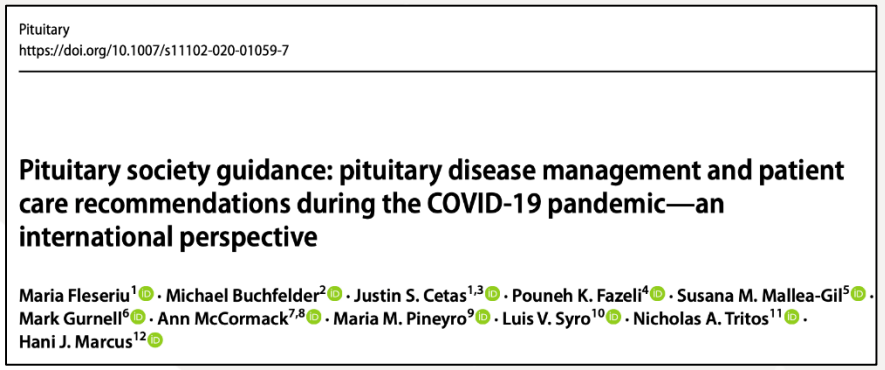

Pituitary
https://doi.org/10.1007/s11102-020-01059-7

Pituitary society guidance: pituitary disease management and patient care recommendations during the COVID-19 pandemic—an international perspective

Maria Fleseriu[1] · Michael Buchfelder[2] · Justin S. Cetas[1,3] · Pouneh K. Fazeli[4] · Susana M. Mallea-Gil[5] · Mark Gurnell[6] · Ann McCormack[7,8] · Maria M. Pineyro[9] · Luis V. Syro[10] · Nicholas A. Tritos[11] · Hani J. Marcus[12]

- Active Cushing's particularly in those with severe hypercortisolism significantly immunosuppressed
- Face-to-face health care attendance should be minimised
  - Regular patient contact remains important
    - Video consultation allows limited physical assessment

1. Newell-Price J, et al. Eur J Endocrinol. 2020;183(1):G1-G7; 2. Fleseriu M, et al. Pituitary. 2020;23(4):327-337.

Management Principles

- Medical therapy preferred to surgery
  - Transsphenoidal pituitary surgery is high risk in COVID-19 setting
- Treatment of co-morbidities is important
  - HTN and DM significant risk factors for adverse outcome with COVID-19
- Local COVID-19 prevalence needs to be considered in guiding management plans and re-evaluated every 2-3 months

Study	Diabetes	Hypertension
Yang (n=52; critically ill)	17%	NR
Guan (n=1,099; hospitalised severe)	16.2%	23.7%
Zhang (n=140; hospitalised)	12%	30%

1. Guan W-J, et al. N Engl J Med. 2020;382(18):1708-1720; 2. Newell-Price J, et al. Eur J Endocrinol. 2020;183(1):G1-G7; 3. Yang X, et al. Lancet Respir Med. 2020;8(5):475-481; 4. Zhang J-J, et al. [published online ahead of print Feb 19, 2020]. Allergy. doi: 10.1111/all.14238.
HTN, hypertension; DM, diabetes mellitus; NR, not reported.

Pre-test probability drives timing of further investigations to make a diagnosis of Cushing's

Garvan Institute of Medical Research

CASE 1

- 28-year old female
- Weight gain
- Irregular menses
- Acne
- No bruising, myopathy, striae
- No HTN, DM, osteoporosis/#
- Normal K+

Low pre-test

CASE 2

- 65-year old male
- Pneumonia (COVID neg)
- New onset DM
- Severe HTN
- Bruising, proximal myopathy
- ↓ K+
- *Past history*: depression (escitalopram), hypercholesterolaemia (atorvastatin), GORD (pantoprazole)

High pre-test

→ Low pre-test: may limit or defer further investigation 3-6 months
→ Moderate/high pre-test: limited investigations

GORD, gastro-esophageal reflux disease; K, potassium; HTN, hypertension; DM, diabetes mellitus.

Limit initial screening tests to minimise laboratory contact for patients (and staff)

- 24-hour, urine-free cortisol (UFC)
- 1 mg overnight dexamethasone suppression test
- Biochemistry (electrolytes, liver)
- Metabolics (BSL, HbA1c)
- FBC

Saliva cortisol may be hazardous to lab staff

CASE 2

24-hour UFC 6530 nmol/day (NR 50-320)

BSL, blood sugar level; FBC, full blood count; HbA1c, hemoglobin A1c; NR, normal range; UFC, urine-free cortisol.

Imaging should focus on identification of ACC or overt ectopic ACTH-dependent Cushing's status

Garvan Institute of Medical Research

In the setting particularly of severe Cushing's in a male patient consider:

- *Low* ACTH – CT adrenals (adrenocortical carcinoma*)

- *High* ACTH – CT chest/abd/pelvis (ectopic* e.g. small cell lung cancer)

**may require urgent surgery or chemotherapy*

CASE 2

24-hour UFC 6530nmol/day (NR 50-320)

ACTH 24 pmol/L (NR <12)

ACTH-dependent hypercortisolism

ACC, adrenocortical carcinoma; ACTH, adrenocorticotropic hormone; CT, computed tomography; NR, normal range; UFC, urine-free cortisol.

Medical treatment is the cornerstone of management while COVID-19 is prevalent

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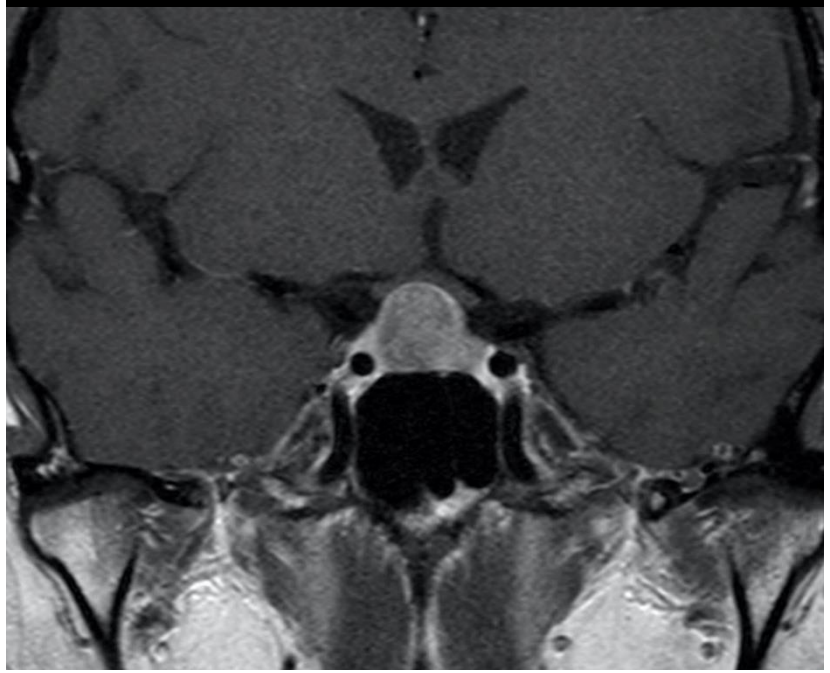
CASE 2

Visual blurring

Coronal T1W MRI demonstrating pituitary macroadenoma



- If there are no visual symptoms, MRI pituitary could be delayed
- Priority should be for prompt medical treatment of hypercortisolism while COVID-19 prevalence remains high

- If visual symptoms or headaches, it may be easier to arrange imaging than formal visuals to assess for macro-adenoma
- CT may be preferred over MRI as faster exam

CT, computed tomography; MRI, magnetic resonance imaging.

High risk of COVID-19 transmission during pituitary surgery

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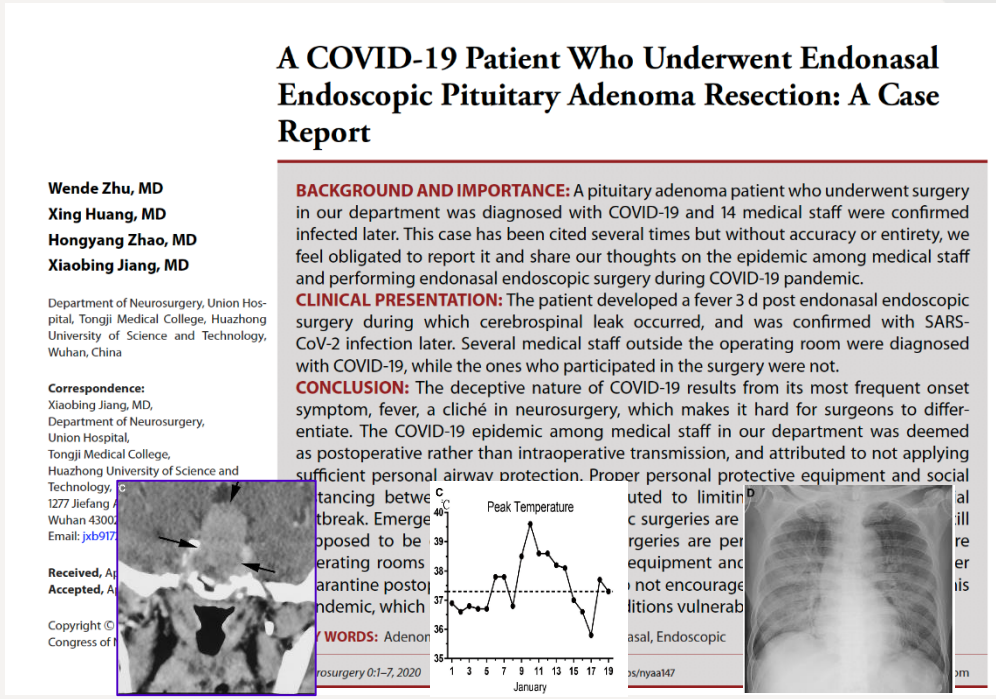

A COVID-19 Patient Who Underwent Endonasal Endoscopic Pituitary Adenoma Resection: A Case Report

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BACKGROUND AND IMPORTANCE: A pituitary adenoma patient who underwent surgery in our department was diagnosed with COVID-19 and 14 medical staff were confirmed infected later. This case has been cited several times but without accuracy or entirety, we feel obligated to report it and share our thoughts on the epidemic among medical staff and performing endonasal endoscopic surgery during COVID-19 pandemic.

CLINICAL PRESENTATION: The patient developed a fever 3 d post endonasal endoscopic surgery during which cerebrospinal leak occurred, and was confirmed with SARS-CoV-2 infection later. Several medical staff outside the operating room were diagnosed with COVID-19, while the ones who participated in the surgery were not.

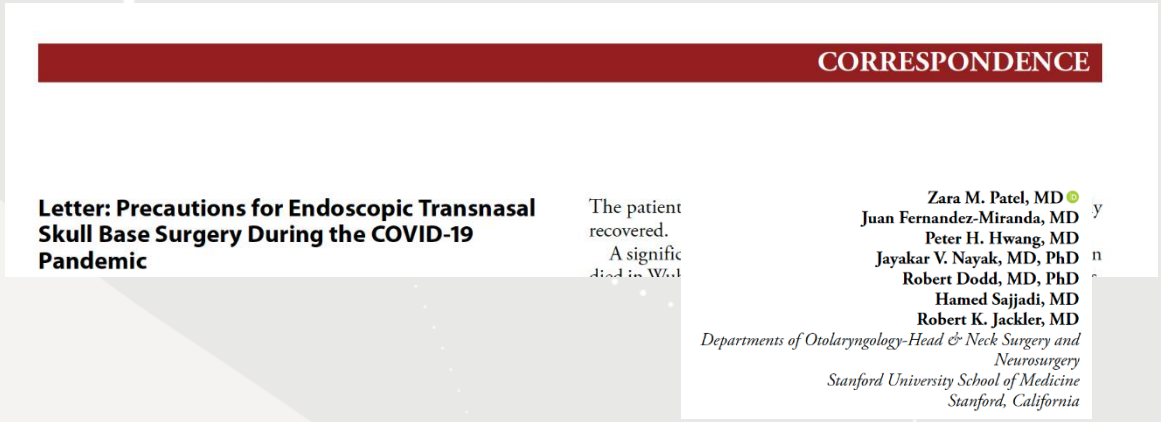
CONCLUSION: The deceptive nature of COVID-19 results from its most frequent onset symptom, fever, a cliché in neurosurgery, which makes it hard for surgeons to differentiate. The COVID-19 epidemic among medical staff in our department was deemed as postoperative rather than intraoperative transmission, and attributed to not applying sufficient personal airway protection. Proper personal protective equipment and social

70-yo male
2/12 visual loss

COVID-19
Diagnosed Jan 19

Death
4 wks postop

14 staff infected in postoperative setting



CORRESPONDENCE

Letter: Precautions for Endoscopic Transnasal Skull Base Surgery During the COVID-19 Pandemic

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- Young male apoplexy (known pituitary tumour) in context of developing COVID-19 infection had endoscopic pituitary surgery

- NS + OR nurses N95 masks → developed COVID
- Anaesthetist positive pressure helmet → neg COVID

Multiple examples Iran & Europe of ENT surgeons performing high-risk nasal and airway procedures contracting COVID-19

1. Zhu W, et al. [published online ahead of print Apr 17, 2020]. Neurosurgery. doi: 10.1093/neuros/nyaa147; 2. Patel ZM, et al. Neurosurgery. 2020;87(1):E66-E67.

ENT, ear, nose & throat; NS, neurosurgeon; OR, operating room.

Indications for surgery in Cushing's Disease when COVID-19 is prevalent

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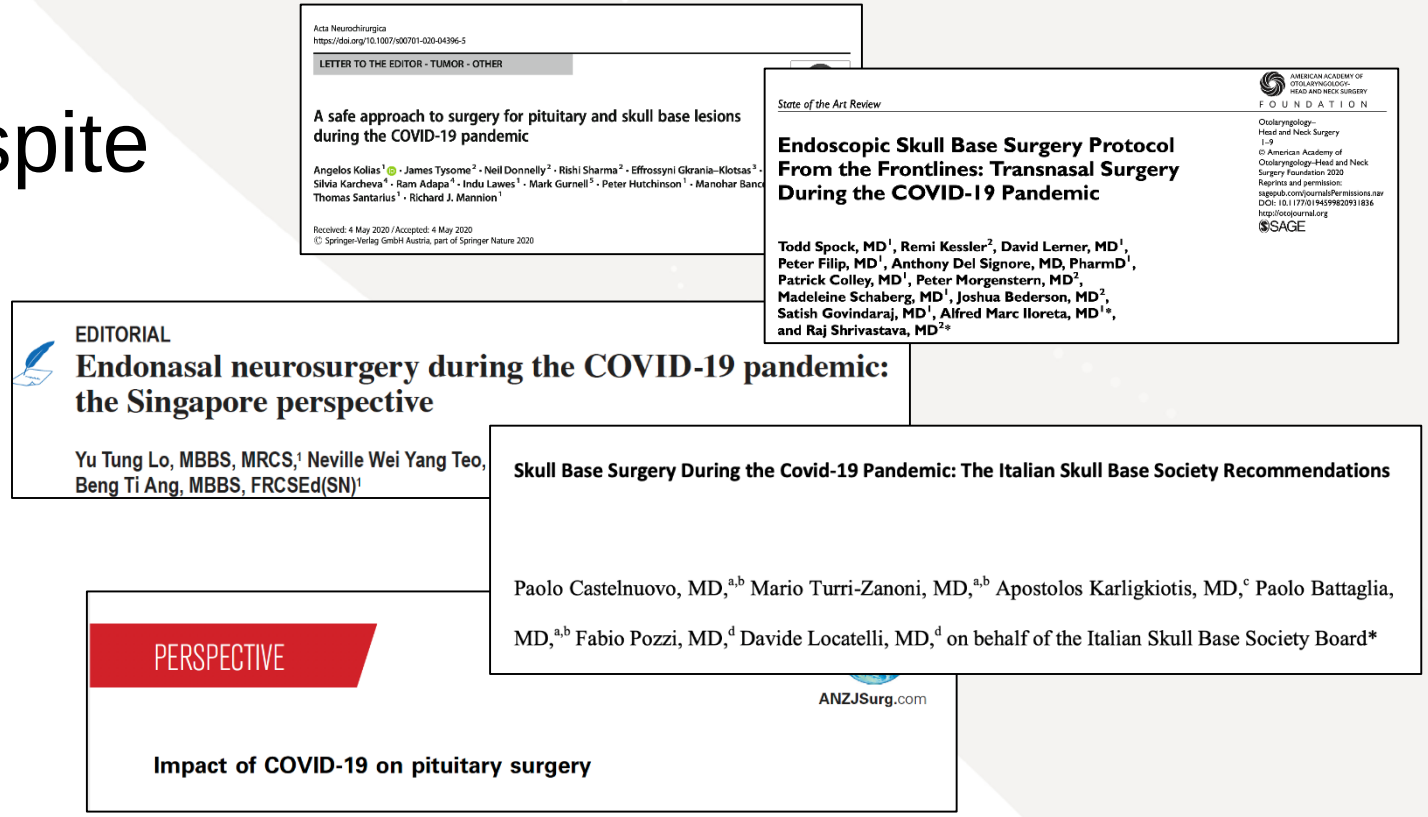
- Very active disease despite medical therapy
- Serious side effects of medical therapy
- Visual compromise
- Pituitary apoplexy



Broad recommendations: defer, pre-operative swab, PPE (transcranial → endoscopic transnasal done safely)

1. Newell-Price J, et al. Eur J Endocrinol. 2020;183(1):G1-G7; 2. Fleseriu M, et al. Pituitary. 2020;23(4):327-337; 3. Castelnuovo P, et al. [published online ahead of print Apr 29, 2020]. Int Forum Allergy Rhinol. doi: 10.1002/alr.22596; 4. Kolias A, et al. Acta Neurochir (Wien). 2020;162(7):1509-1511; 5. Mitchell RA, et al. ANZ J Surg. 2020;90:963–964; 6. Spock T, et al. [published online ahead of print May 26, 2020]. Otolaryngol Head Neck Surg. doi: 10.1177/0194599820931836; 7. Tung Lo Y, et al. [published online ahead of print Apr 17, 2020]. J Neurosurg. doi: 10.3171/2020.4.JNS201036.
PPE, personal protective equipment.

Steroidogenesis inhibitors* (**ketoconazole, metyrapone, osilodrostat**) will be mainstay of medical therapy for most patients

Ketoconazole	Concern around drug-drug interactions, liver toxicity and need for gastric acid for activity
Metyrapone and osilodrostat	May potentiate hypokalaemia
Dopamine agonist	Trial for mildest cases
Pasireotide	May cause glycaemic deterioration
Glucocorticoid receptor antagonist (mifepristone)	Difficult to titrate and indicated for unstable diabetes or hypertension

*Country-specific availability

1. Newell-Price J, et al. Eur J Endocrinol. 2020;183(1):G1-G7; 2. Fleseriu M, et al. Pituitary. 2020;23(4):327-337; 3. Feelders RA, et al. J Clin Endocrinol Metab. 2013;98:425-438

Adverse effects and need for monitoring are considerations in choice of medical therapy

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CASE 2

- Commenced on metyrapone 250mg tds
  - Caution: ketoconazole – escitalopram and atorvastatin interactions; on PPI
- Aim for morning pre-dose cortisol 250-330 nmol/L
  - Err on side of slight cortisol excess rather than risk adrenal insufficiency
  - Consider more clinical assessment to reduce frequency of biochemical testing

UFC cannot identify overtreatment on metyrapone

Measurement via mass spectrometry preferred to avoid cross-reactivity with cortisol metabolites on standard immunoassay platforms

PPI, proton-pump inhibitor; tds, 3 times a day; UFC, urine-free cortisol.

Active management of co-morbidities important

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CASE 2

- Aggressive antihypertensive and diabetes management
- DVT prophylaxis (LMW heparin)
- Potassium supplementation
- Prophylaxis against *Pneumocystis jivoreci* with trimethoprim/sulfamethoxazole
- Instructed on sick day management, provided with stress dosing glucocorticoid and emergency injectable hydrocortisone

Consider initiation of alternative antihypertensive agents to ACEi or ARBs?

However multiple recent studies[1] **DO NOT** provide evidence of harm with ACEi or ARB use with risk of COVID-19 infection or severe disease

Use stress glucocorticoid therapy if becomes infected with COVID-19

1. Jarcho JA, et al. N Engl J Med. 2020;382:2462-2464.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DVT, deep-vein thrombosis; LMW, low-molecular-weight

What are the options with ongoing active disease?

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CASE 2

- Morning cortisol 800-900 nmol/L despite metyrapone 3 g/day
- BP and BSL remain difficult to control
- Decision made to proceed to urgent surgery
  - Reduced local COVID-19 prevalence

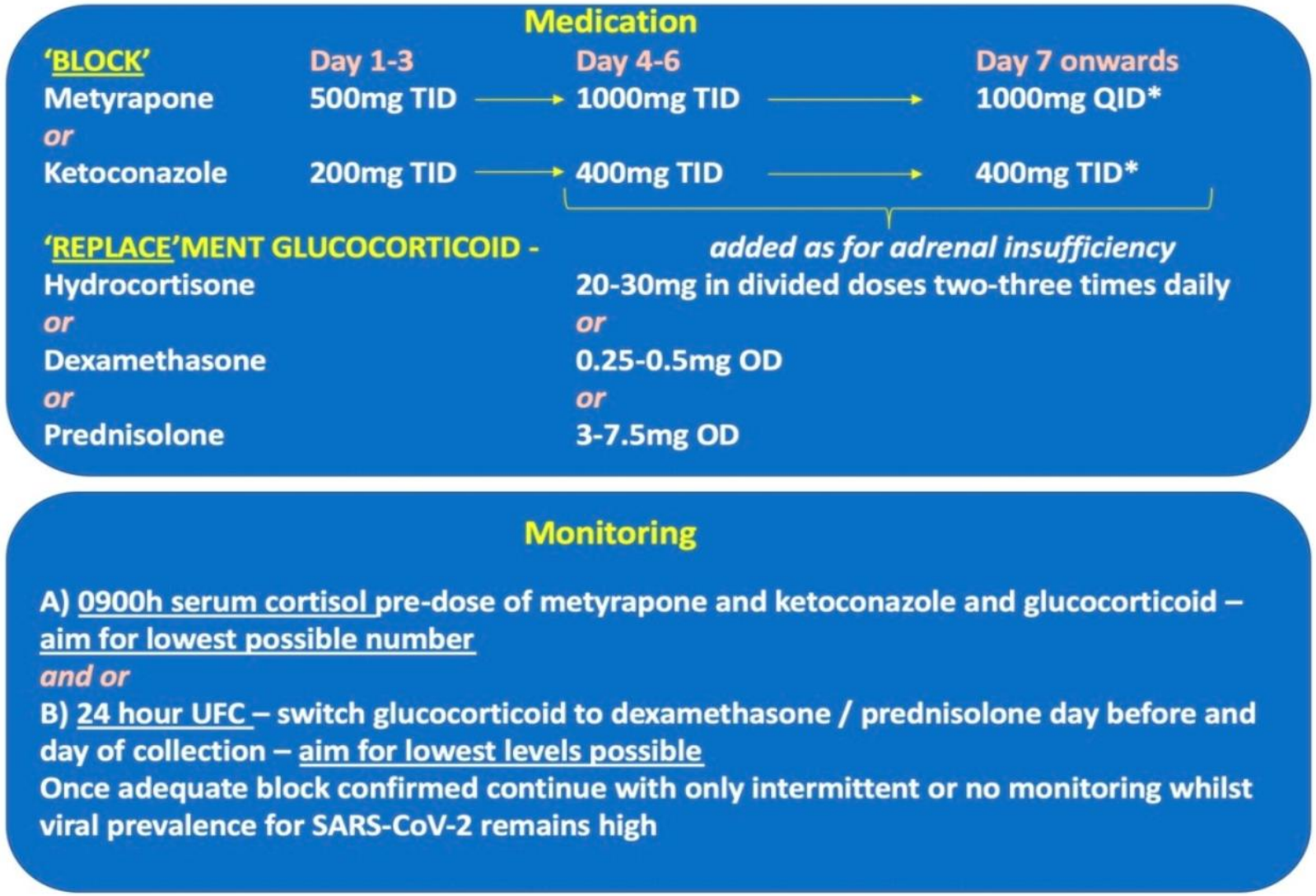
OTHER OPTIONS

COMBINATION THERAPY
e.g. ketoconazole – requires frequent LFT monitoring

"BLOCK AND REPLACE"
Reduces risk of adrenal insufficiency
May enable less frequent monitoring

BP, blood pressure; BSL, blood sugar level; LFT, liver function test.

A “block and replace” regime



*doses may be increased further if needed and ketoconazole and metyrapone may be used in combination; with monitoring, it may also be possible to reduce the dose while maintaining blockade – collaboration with expert in Cushing’s is recommended

1. Newell-Price J, et al. Eur J Endocrinol. 2020;183(1):G1-G7.
OD, once a day; QID, 4 times a day; TID, 2 times a day; UFC, urine-free cortisol.

Regular clinical review imperative in these times

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CASE 1

- Reviewed after 3 months via video consult
  - Ongoing high local prevalence COVID-19
- Clinically unchanged
- UFC: 330 nmol/d (NR 50-320)
- ONDST: postdex cortisol 65nmol/L (N <50)
- ACTH 9 pmol/L (NR <12)
- Commenced on cabergoline 0.5 mg/week
  - Further investigation postponed

ACTH, adrenocorticotropic hormone; NR, normal range; ONDST, overnight dexamethasone suppression test; UFC, urine-free cortisol.

Case Studies

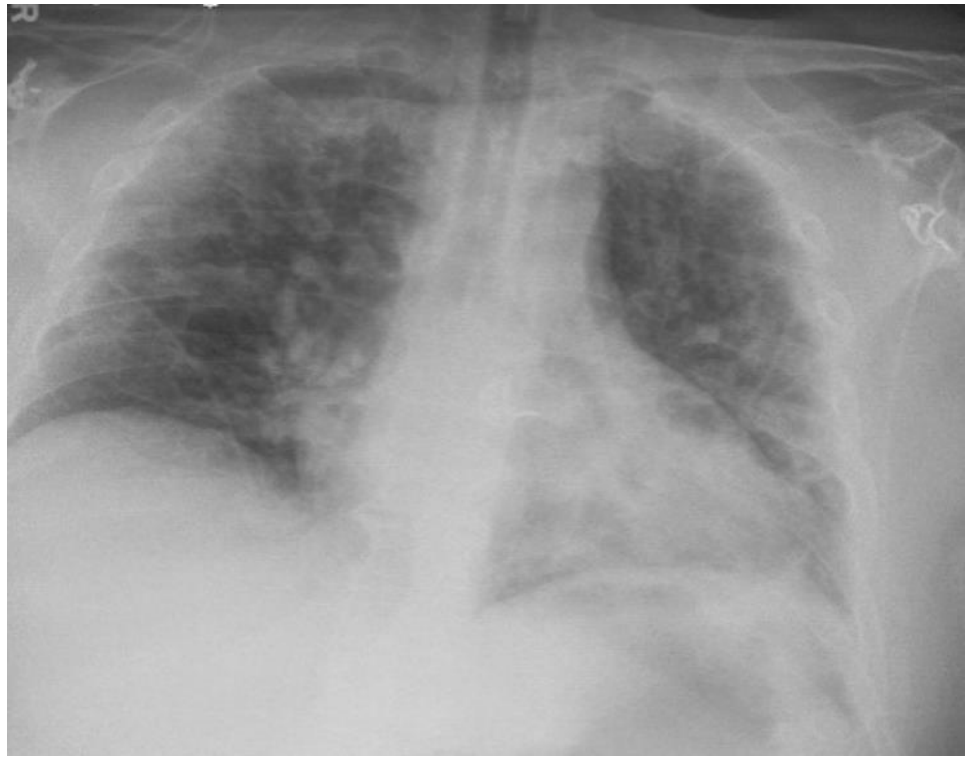
OREGON HEALTH & SCIENCE UNIVERSITY

Case Study 1: COVID-19 diagnosis, a good thing in disguise?

Stuti Fernandes, MD, Maria Fleseriu, MD, FACE
Pituitary Center
Oregon Health & Science University,
Portland, Oregon

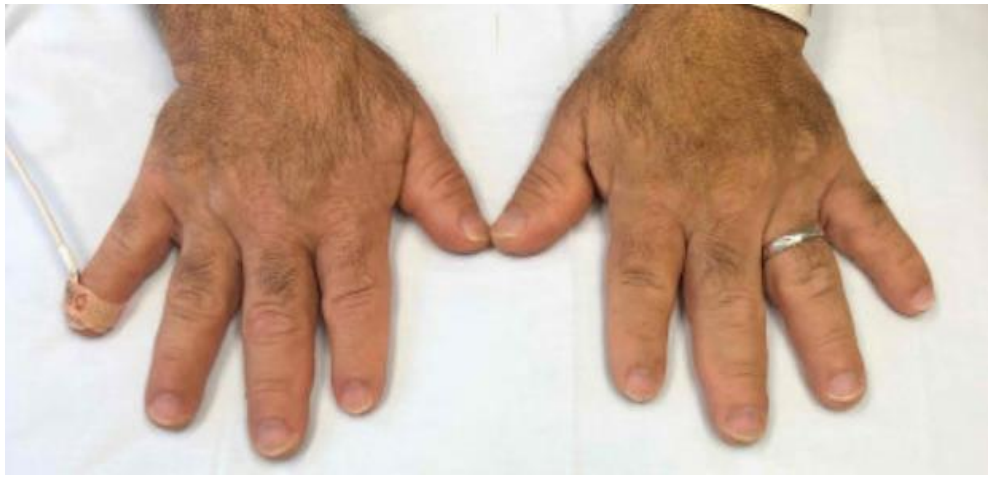
Case presentation

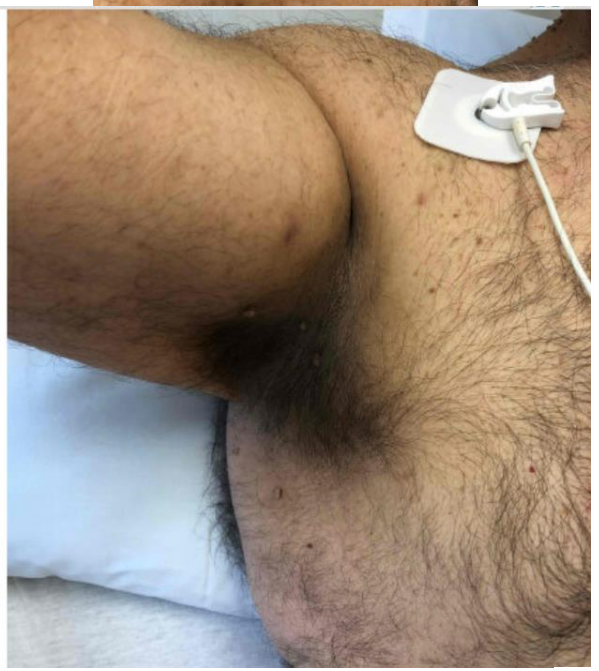
- 47 year old male presented to the ER with cough, dyspnea and syncope.
- **COVID-19 positive** with multi-focal pneumonia on imaging.
- Past medical history untreated pre-diabetes and sleep apnea (not using CPAP).
- Hospitalist noticed patient had suspicious features for GH excess.



CPAP, continuous postivie airway pressure; GH, growth hormone.

Physical Exam





History

- Increased size of hands, feet and jaw over 4-5 years
- Feet changed from size 10 to 12
- Ring size increased
- Increased fatigue in the past 2 years
- Gained 70 pounds (approx. 32 kg) over the past 8 years
- No perceived change in peripheral vision
- Infrequent headaches
- No family history of endocrine disorders

Laboratory Findings

- **IGF-1 447 ng/mL (71-224)**
- **GH 29.30 ng/mL (0.03-3.00)**
- FSH 9 mIU/mL (< 18)
  LH 7 mIU/mL (< 10)
  testosterone 87 ng/dL (300-890)
- Prolactin 21.7 ng/mL (2.1-17.7)
- TSH 1.94 mIU/L (0.44-4.75)
  free T4 1.0 ng/dL (0.6-1.2)
- ACTH 62 pg/mL (<45)
- Cortisol (AM) 20.2 ug/dL (> 12)
- HbA1c 6.1 % (< 5.7)

Acromegaly confirmed
Central hypogonadism, no other pituitary dysfunction

Patient was in a hospital setting, thus laboratory work-up was facilitated

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; HbA1C, glycosylated haemoglobin A1C ;IGF-1, insulin-like growth factor-1;LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

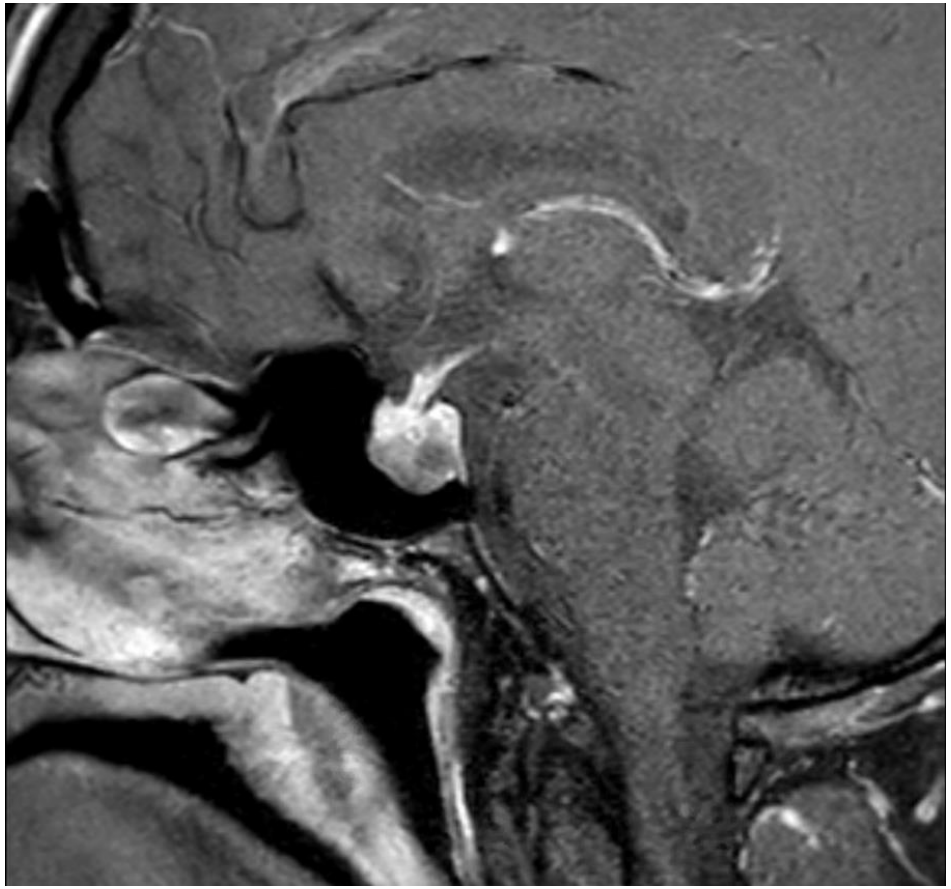
Further plan

Topics for discussion

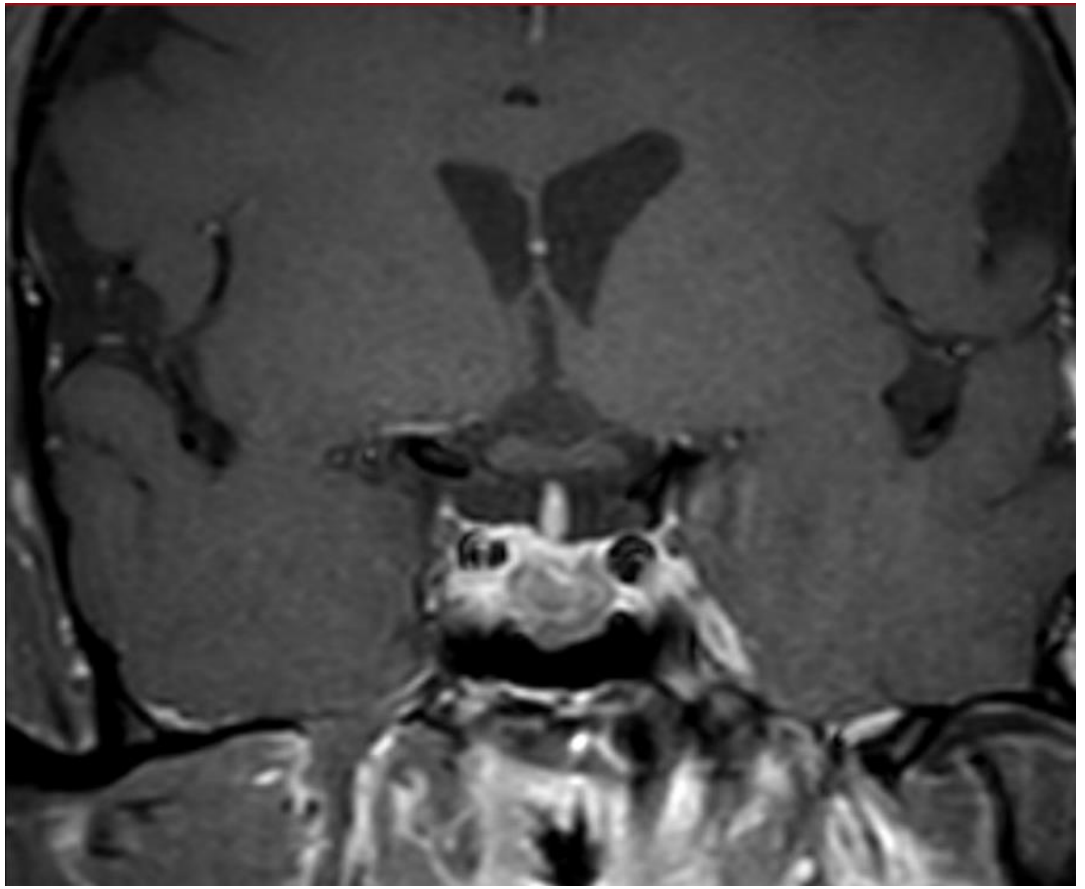
- No headaches, no visual field abnormalities, should we do imaging now?
- CT or MRI, with or without contrast?
- If patient presented to outpatient clinic with COVID-19, should he have been sent to lab for further biochemical work-up and/or imaging?

CT, computed tomography; MRI, magnetic resonance imagining.

MRI Pituitary



Pituitary tumor, MRI sagittal view



Pituitary tumor, MRI coronal view

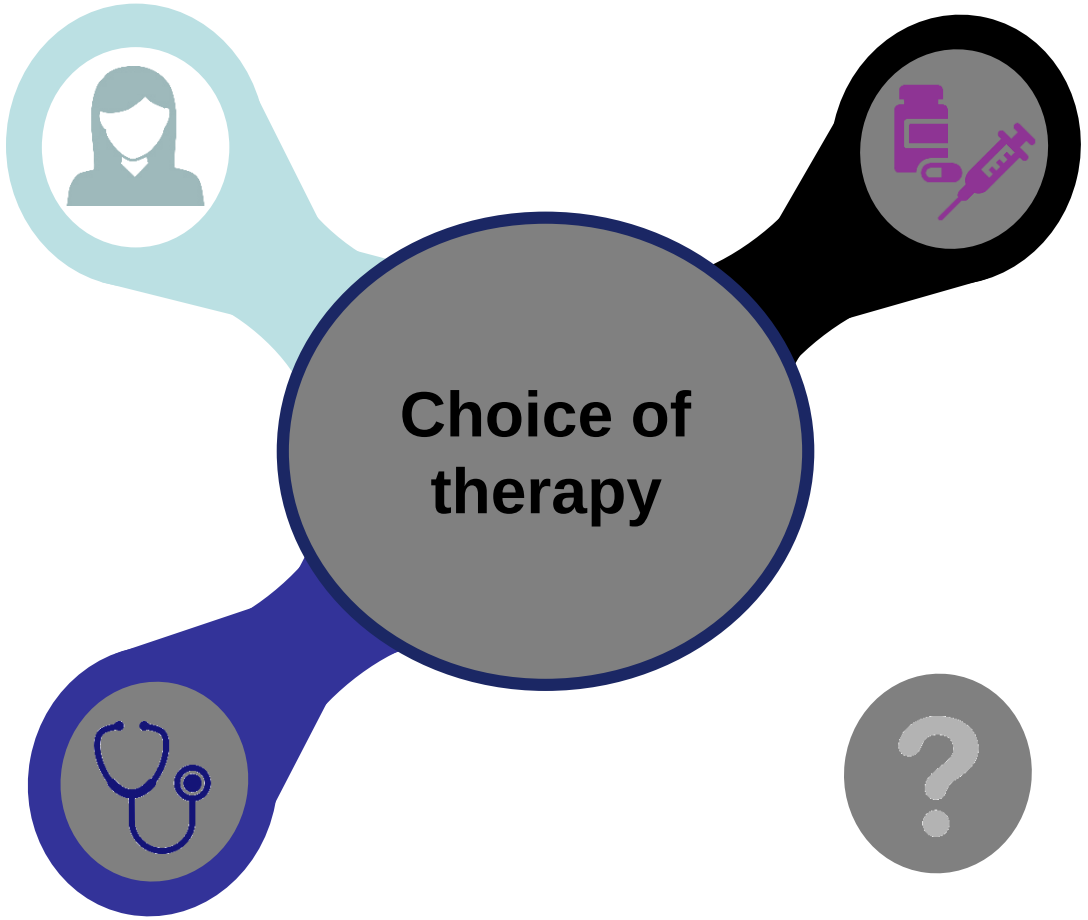
Treatment decision making : What should be considered?

Patient factors

Patient wishes

Medical history

Concomitant medications



Treatment factors

Efficacy profile and speed of action

Safety profile

Self administration

Disease factors

Severity

Comorbidities

Availability

Costs

Clinical Course

- Hydroxychloroquine per COVID-19 protocol at that time
- Supplemental oxygen with nasal canula
- Concern for soft tissue swelling potentially causing respiratory compromise

Treatment for GH excess:

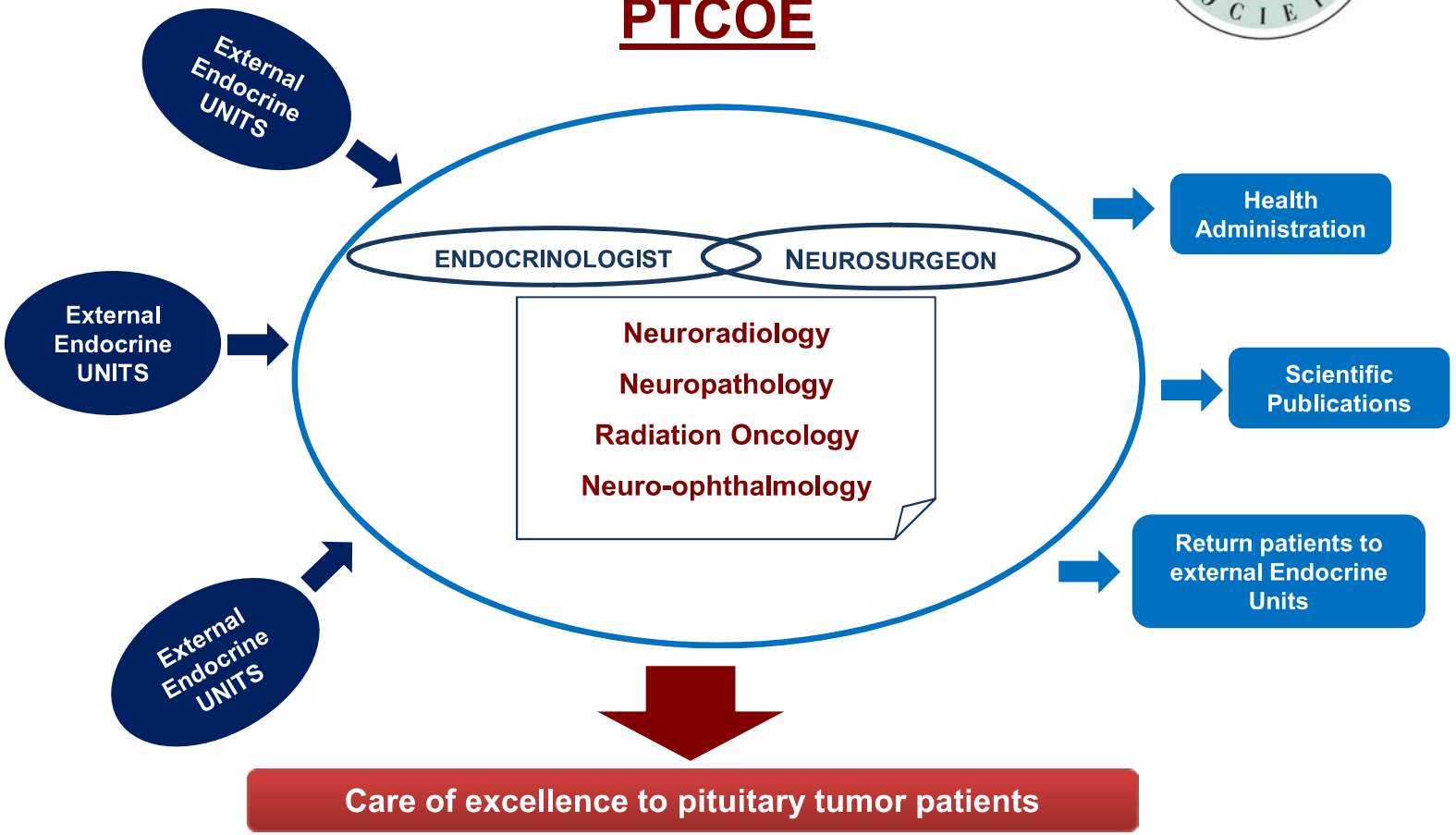
- Based on hospital pharmacy availability, started **octreotide 50 mcg b.i.d.**
  - t.i.d. was initially planned, chose reduced frequency to use less protective equipment
- Patient had significant improvement of symptoms on octreotide
  - Plan to change to lanreotide with self injection at home after discharge
- Surgery planned when feasible based on COVID-19 hospital restrictions and response to medical therapy

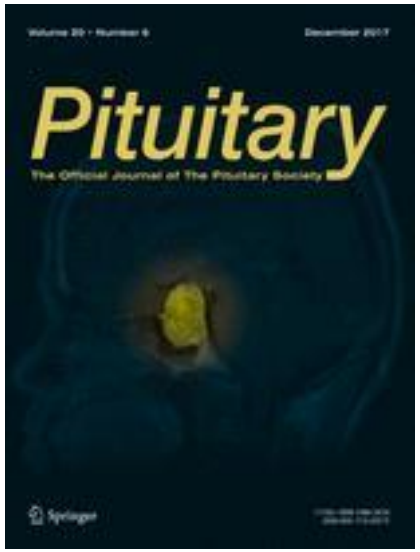
b.i.d, twice daily; GH, growth hormone;; t.i.d, three-times daily.

Pituitary (2017) 20:489–498
DOI 10.1007/s11102-017-0838-2

PITUITARY SOCIETY POSITION STATEMENT

Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): A Pituitary Society Statement



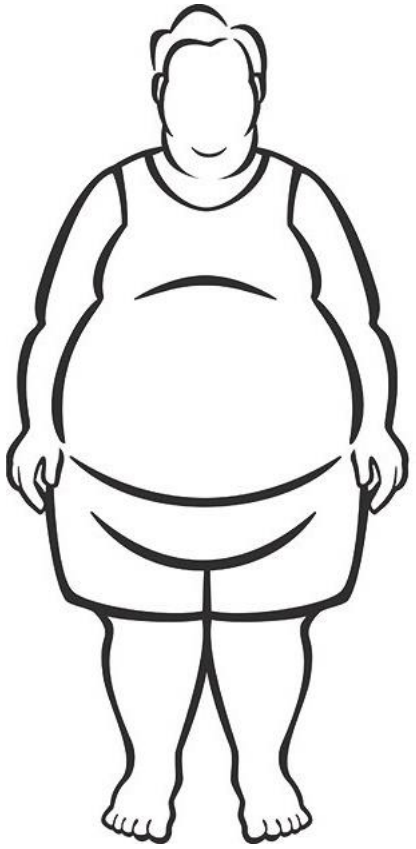


Casanueva FF et al. *Pituitary*. 2017;20(5):489-498.


Thank you!
Questions?

Case Study 2

Juanita Silva-Serrano, MD,
Mario Morales-Esponda, MD, Francisco J. Gómez-Pérez, PhD, Daniel Cuevas-Ramos, PhD.
Department of Endocrinology and Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.



49 yo female with a history of type 2 diabetes, hypertension and primary hypothyroidism

Chief complaint: **weight gain.**

She was extremely obese at the time of the first visit (BMI of 57 kg/m^2).

Two years prior to presentation she had also developed **proximal muscle weakness**, **dorsocervical fat** and **alopecia.**

Screening tests for Cushing‘s syndrome were performed.

Biochemical evaluation:

Urinary free cortisol (UFC) 693 µg/24 h

Serum cortisol after LDDST 12 µg/dL

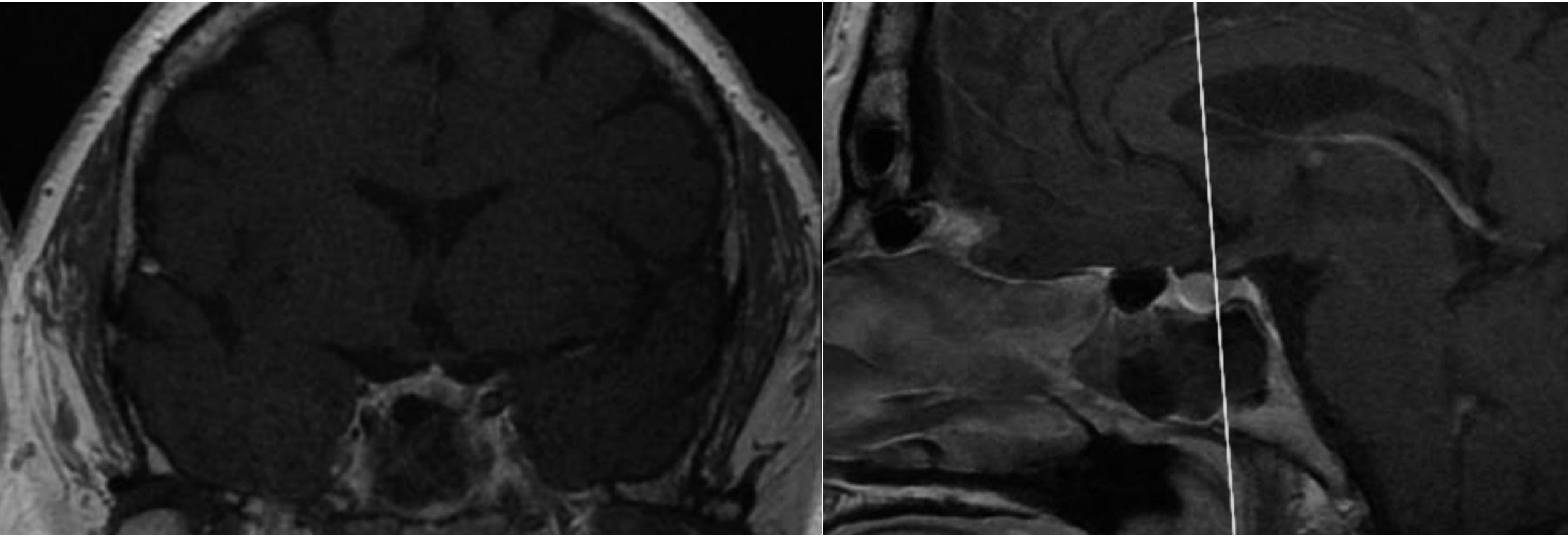
**ACTH concentration was 40 pg/mL.

HDDST were compatible with Cushing‘s disease, and pituitary MRI revealed a 5 mm microadenoma

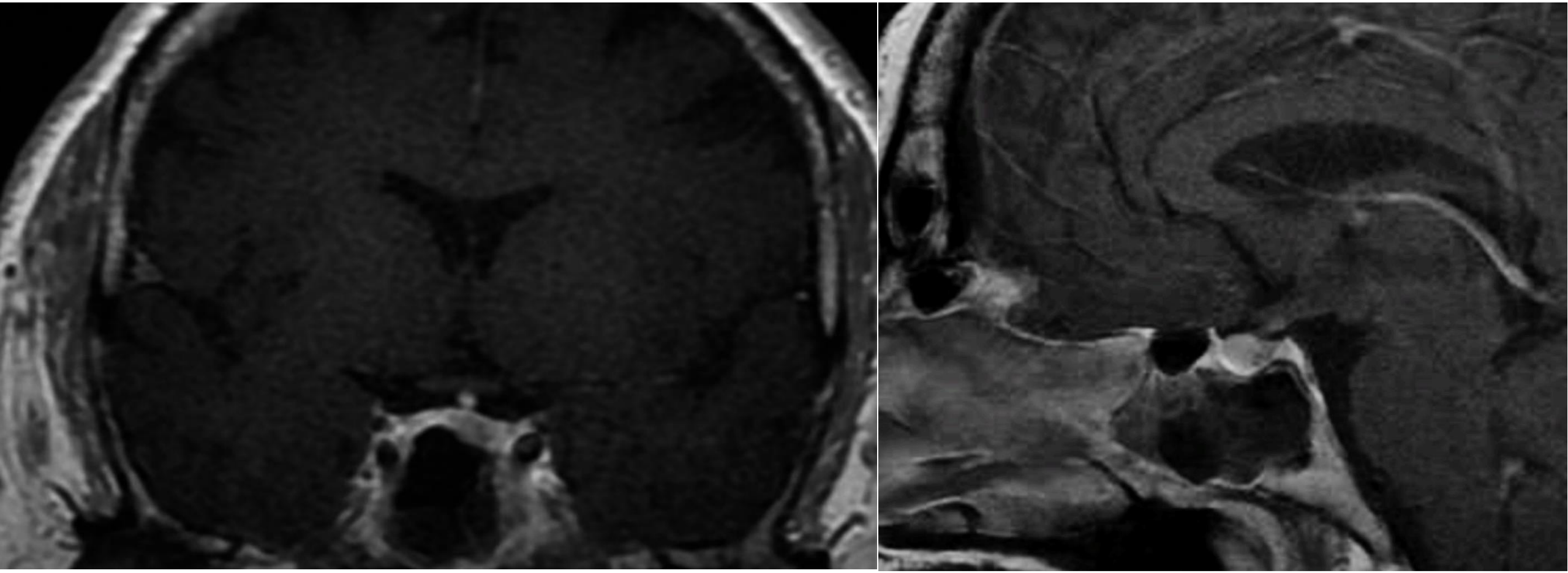
Ketoconazole was started and progressively increased until maximal effective dosage was achieved (**1200 mg/day**).
Cabergoline was added at a dose of 1 mg/week.

***Biochemical evaluation at last follow-up**

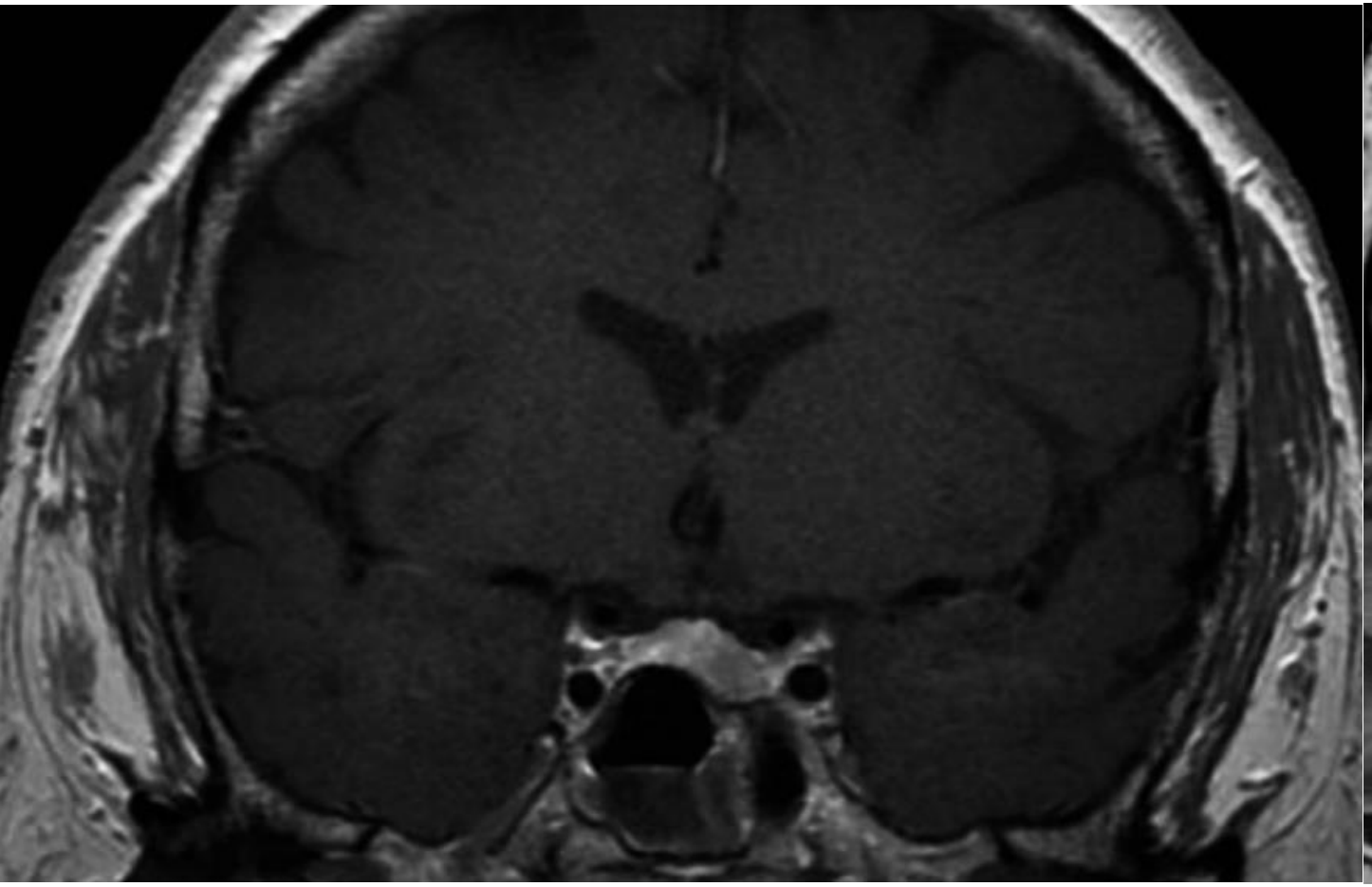
Fasting glucose 95 mg/dL	HbA1C 6.2%
Potasium 4.2 mEq/L	TSH 1.35 mIU/L,
ALT 11.6 U/L	Free thyroxine 0.9 ng/dL
AST 17.8 U/L	**UFC 557 µg/24 h**

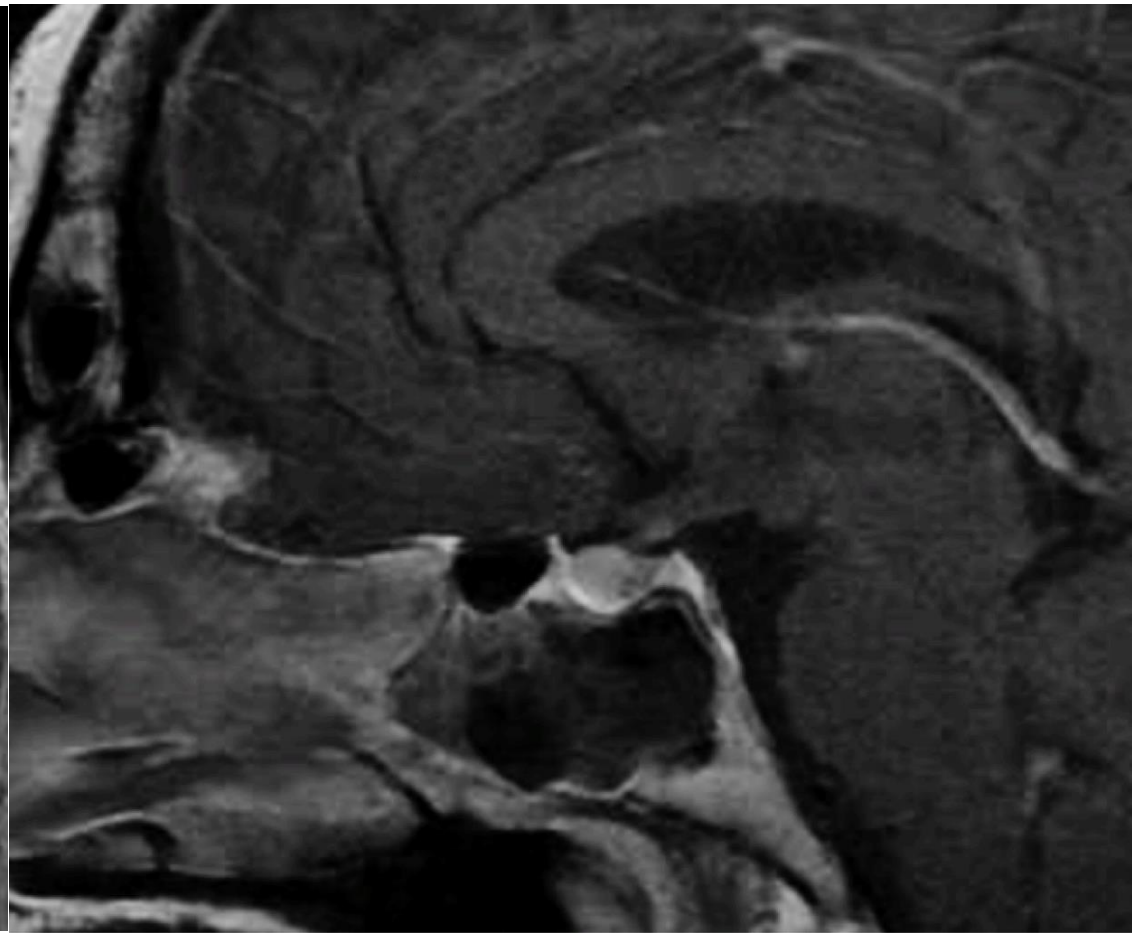


MRI 2019



MRI 2020





MRI 2020

Questions

In view of unintended surgical delay associated with COVID-19 pandemic and poorly controlled hypercortisolism, we have considered radiotherapy as a first line therapy for this case.

In this scenario, **would you consider withdrawing ketoconazole before RT in order to improve efficacy,** or would withdrawal impose too high a risk of severe complications related to hypercortisolism?

Questions

Would you rather perform surgery in this specific case? In view of TSE adenomectomy being a procedure that could result in aerosol formation and an increased risk of SARS-CoV2 transmission, **what kind of surgical approach would you recommend?**


INSTITUTO NACIONAL DE
MEDICAS Y NUTRICION
SALVADOR ZUBIRAN

¡Gracias!

Q&A