Apoplexy in a previously undiagnosed pituitary macroadenoma in the setting of recent COVID-19 infection

Su-Yi Liew,[1] Rachel Seese,[1] Abdulrahman Shames,[1] Kalpita Majumdar[2]

[1]Barts Health NHS Trust, London, UK
[2]Diabetes and Endocrinology, Barts Health NHS Trust, London, UK

Correspondence to
Dr Abdulrahman Shames; abdul_shames@hotmail.co.uk

Accepted 16 July 2021

SUMMARY

Pituitary apoplexy is an endocrine emergency, which commonly presents as hypopituitarism. Prompt diagnosis and treatment can be both life and vision saving. There are a growing number of published case reports postulating a link between COVID-19 and pituitary apoplexy. We report the case of a 75-year-old man who presented with a headache and was later diagnosed with hypopituitarism secondary to pituitary apoplexy. This occurred 1 month following a mild-to-moderate COVID-19 infection with no other risk factors commonly associated with pituitary apoplexy. This case, therefore, supplements an emerging evidence base supporting a link between COVID-19 and pituitary apoplexy.

BACKGROUND

Pituitary apoplexy is a clinical syndrome caused by haemorrhagic or ischaemic necrosis of the pituitary gland, often occurring in pituitary adenomas.[1] The pituitary gland (hypophysis) consists of an anterior lobe (adenohypophysis) and a posterior lobe (neurohypophysis). The adenohypophysis secretes growth hormone (GH), adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinising and follicle-stimulating hormone (LH/FSH) and prolactin. The neurohypophysis releases oxytocin and antidiuretic hormone.

The pituitary gland has a rich and complex vascular supply, making it more susceptible to haemorrhage. Blood vessels within pituitary adenomas may have low fenestration, incomplete maturation and fragmented basal membranes that contain perivascular spaces filled with red cells and plasma proteins, which could predispose to haemorrhage. Indeed, pituitary tumours have a 5× greater risk of bleeding compared with other brain tumours due to the glands rich vascularity.[2] Rapid growth of a tumour and increased metabolic activity which outpaces the development of sufficient blood supply to a tumour creates increased demand, which may precipitate pituitary apoplexy.[3]

Pituitary apoplexy is a medical and surgical emergency due to its association with both hormonal dysregulation, in addition to cerebral ischaemia, subarachnoid haemorrhage, brain strokes and death. Prompt recognition and treatment is therefore vital. This case describes an atypical case of pituitary apoplexy in an otherwise healthy man as it was not preceded by commonly known risk factors which include hypertension, anticoagulant therapy, major surgery and head trauma, and makes possible the link between novel coronavirus infection and an apoplectic event.[4]

A growing number of case reports have been published, which propose a link between pituitary apoplexy and concomitant or preceding COVID-19 infection. Although there are an increasing number of reports, literature remains scarce on this topic and therefore each case builds our collective knowledge and helps identify previously unknown associations and risks.

COVID-19 is a highly contagious and often lethal virus. It is complex and even after recovery, can have a devastating effect on patients' lives. While there have been great advances in our understanding of COVID-19 within a very short span of time, much is still unknown. With COVID-19 still prevalent across the UK and many other parts of the world, it is important to consider the possible effects on more rare medical presentations. A number of case reports have been published which propose a link between pituitary apoplexy and COVID-19. As such we believe COVID-19 was likely to be a causative factor in the development of pituitary apoplexy in this instance.

CASE PRESENTATION

A 75-year-old man was referred to hospital by his general practitioner (GP) for investigation of suspected hypopituitarism. He was usually well, with a medical history of irritable bowel syndrome and a previous Mallory-Weiss tear.

Recent medical history consisted of a COVID-19 infection approximately 6 weeks prior to his current presentation to hospital. At the time, the patient had attended Accident and Emergency with symptoms of increasing shortness of breath on exertion and an 8-day history of a dry cough. A nasopharyngeal swab was positive for SARS-CoV-2 RNA. Chest X-ray showed bilateral mid to lower zone shadowing, in keeping with COVID-19 infection. Oxygen saturations were 96% on room air, dropping to 92%–93% on ambulation. Arterial blood gas (on room air) showed that the patient was mildly hypoxaemic (table 1). C reactive protein was raised and he was mildly hypokalaemic, but blood results were otherwise unremarkable (table 1). The patient elected to self-discharge from hospital against medical advice, he did not receive any treatment during his time in hospital.

One month later, the patient attended hospital following a sudden onset of severe frontal headache and a 1-week history of fevers up to 40°C.

To cite: Liew S-Y, Seese R, Shames A, *et al*. *BMJ Case Rep* 2021;**14**:e243607. doi:10.1136/bcr-2021-243607

Table 1 ABG and blood results from first hospital admission

Test	Result	Reference range
pH	7.46	7.35–7.45
pO_2 (kPa)	9.51	11.0–14.0
pCO_2 (kPa)	4.34	4.70–6.40
Bicarbonate (mmol/L)	24.6	22.0–29.0
Lactate (mmol/L)	0.9	0.4–0.8
White cell count (x10^9/L)	4	4.0–10.0
Neutrophils (x10^9/L)	2	2.0–7.0
Lymphocytes (x10^9/L)	1.3	1.0–3.0
Sodium (mmol/L)	137	133–146
Potassium (mmol/L)	3.2	3.5–5.3
CRP (mg/L)	48	≤5

CRP, C reactive protein.

Additionally, he described feeling increasingly drowsy and 'out of it', and reported a 3-day history of constipation. On examination, the patient was noted to be drowsy and somewhat slow to answer questions; however, was fully orientated and Glasgow Coma Score was 15. There was periorbital tenderness to palpation. Cranial nerve and peripheral neurological examinations were normal, and review of systems did not reveal any obvious source of infection that would explain the patient's fever.

Blood tests revealed that he was hyponatraemic but measured electrolytes were otherwise all within range. CRP was raised, however, white cell count was normal (table 2). The patient did not have a COVID-19 swab on this admission. Chest X-ray appearance was unremarkable.

The headache was attributed to a likely underlying viral infection and dehydration. He was discharged with a course of coamoxiclav and metronidazole for treatment of suspected diverticulitis and advised to reseek medical advice if his symptoms were to get worse.

The patient's GP arranged for further blood tests in the community to investigate ongoing symptoms of lethargy and drowsiness. The results revealed a picture consistent with anterior panhypopituitarism, as evidenced by dysfunction of the pituitary–adrenal; pituitary–thyroid and pituitary–gonadal axes (table 3). The patient was referred to hospital for urgent investigation and treatment. Ideally, serum ACTH level would have been measured to confirm secondary hypoadrenalism, however, this was unfortunately not done at the time.

On admission, the patient reported persistent symptoms of increasing lethargy and tiredness, however, the headache had now resolved. He was additionally reporting memory loss, feeling light-headed when standing, as well as peripheral oedema. Lying and standing blood pressure was not performed. The patient was clear that these symptoms were of recent onset. Systemic examination looking for stigmata of endocrine disease revealed no evidence of chronic pituitary insufficiency. There was no preceding history of reduced frequency of shaving or sexual dysfunction, and he had normal distribution of body hair, all suggestive that the low testosterone level was of recent onset. There was no neurological or visual field deficit on the examination.

Table 2 Blood results from second admission to hospital

Test	Result	Reference range
White cell count (x10^9/L)	6.5	4.0–10.0
Sodium (mmol/L)	132	133–146
Potassium (mmol/L)	4.2	3.5–5.3
CRP (mg/L)	16	≤5

CRP, C reactive protein.

Table 3 Blood results from third admission to hospital

Test	Result	Reference range
White cell count (x10^9/L)	5.4	4.0–10.0
Sodium (mmol/L)	128	133–146
Potassium (mmol/L)	4.3	3.5–5.3
CRP (mg/L)	29	≤5
Random serum glucose (mmol/L)	5.7	<11.1
9am serum cortisol (nmol/L)	57	133–537
Free T4 (pmol/L)	6.9	10.5–24.5
Thyroid-stimulating hormone (mU/L)	0.1	0.27–4.2
Testosterone (nmol/L)	<0.5	6.7–25.7
Luteinising hormone (unit/L)	<1.0	1.7–8.6
Prolactin (mU/L)	64	0–323
Insulin-like growth factor 1 (µg/L)	37	21.9–215.8

CRP, C reactive protein.

The patient was started on intravenous hydrocortisone replacement pending further investigations.

INVESTIGATIONS

Imaging was performed to investigate for suspected pituitary apoplexy with an underlying pituitary adenoma. CT imaging demonstrated a rounded mass within the pituitary fossa 11 mm in diameter and of increased attenuation than the adjacent brain. The average attenuation value of the lesion was measured as 65 HU, which corresponds with a fresh blood clot (less than 1 week) (figure 1).

A subsequent MRI scan performed 2 days later revealed a 12 mm mass located anteriorly within the pituitary gland, extending upwards into the suprasellar cistern but not compressing the optic chiasm. Within the pituitary there was a large area of high signal on T1-weighted imaging consistent with the presence of methaemoglobin. The MRI appearance of fresh blood clot is complex due to gradual decomposition of the haematoma in the sequence oxyhaemoglobin, deoxyhaemoglobin, methaemoglobin and haemosiderin. Only methaemoglobin causes increased signal on T1-weighted images. The low signal crescent adjacent to the area of increased signal may represent either deoxyhaemoglobin or methaemoglobin as not all areas of a haematoma decompose at the same rate (figure 2). The MRI appearances were consistent with haemorrhage into a pre-existing pituitary macroadenoma, confirming pituitary apoplexy.

The MRI images also showed an incidental finding of a small area of high signal in the left occipital lobe, with appearances suggestive of a subacute infarct. However, the images were later reviewed by a stroke medicine consultant who advised that there was no evidence of stroke.

Formal assessment of the patient's visual fields showed no deficit.

OUTCOME AND FOLLOW-UP

Following the commencement of hydrocortisone, thyroid replacement was started in the form of levothyroxine. Serum sodium levels normalised following initiation of medical treatment. He did not require testosterone replacement as he did not have any symptoms or signs of hypogonadism. The patient was followed up 2 weeks postdischarge. He reported feeling

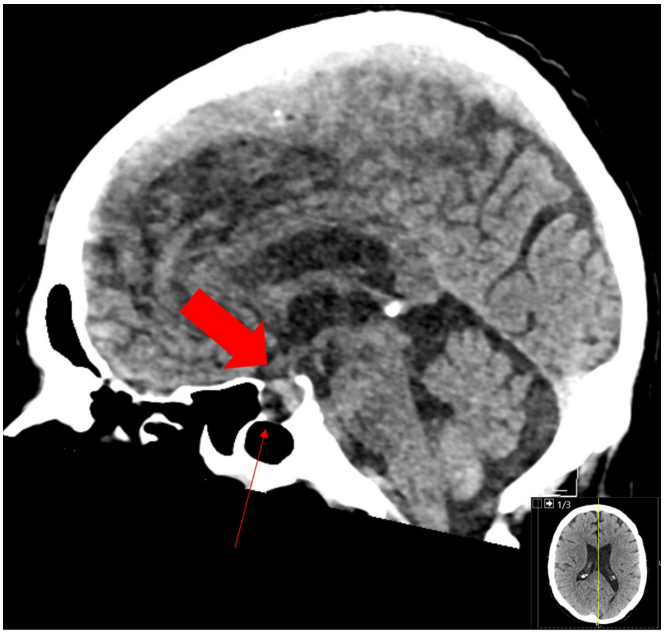

Figure 1 Sagittal reformat of CT scan showing high attenuation mass in pituitary fossa (large arrow). Note that a low attenuation artefact due to beam hardening from adjacent bone obscures the anteroinferior portion of the pituitary fossa (small arrow).

'renewed' with the medications, saying that his energy levels were better, and his ankle oedema had resolved. A follow-up MRI scan showed reduction in the size of the haemorrhagic lesion (figure 3).

The case and imaging was reviewed at the tertiary endocrinology multidisciplinary team meeting. There was a consensus that no neurosurgical input was required immediately, and a decision was made to continue with hormone replacement therapy and to monitor the pituitary macroadenoma with a repeat MRI after 6 months.

DISCUSSION

COVID-19 has posed a multitude of challenges to the medical profession, and our understanding of how it affects different bodily systems remains incomplete. Pituitary apoplexy

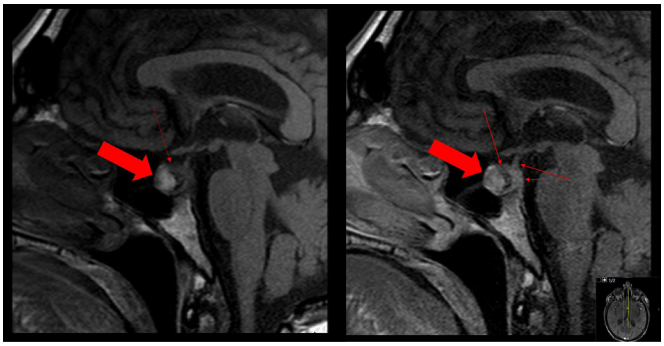

Figure 2 Unenhanced (left) and contrast-enhanced (right) T1-weighted sagittal MRI scans demonstrate an area of high signal within the enlarged pituitary gland due to methaemoglobin (large arrow) and a smaller crescentic area of the haematoma at a different stage of evolution (small arrow). There is normal enhancement of the compressed pituitary tissue and pituitary stalk (paired arrows right image).

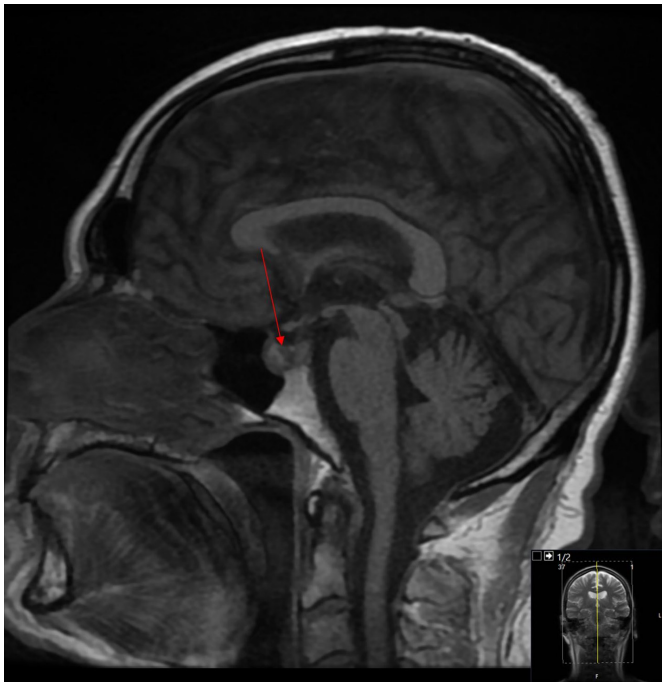

Figure 3 Follow-up T1-weighted sagittal MRI scan demonstrates reduction in size of the haematoma with change in superior aspect of pituitary gland from convex to concave (arrow).

constitutes an endocrine emergency which requires prompt recognition and management. This case demonstrates a potential link between COVID-19 infection and pituitary apoplexy, although this remains speculative at this point in time. Known risk factors for pituitary apoplexy include, but are not limited to, pituitary adenoma, angiography, orthopaedic and cardiac surgery, anticoagulation, pituitary dynamic testing and hypotension and hypertension.[5] Despite this, over 50% of apoplexy has no understood or discovered precipitating event.[6]

Our case of a normally well man presenting with pituitary apoplexy in the context of undiagnosed pituitary adenoma and recent COVID-19 infection contributes to the growing number of similar acknowledged cases. The relationship between overwhelming infection inciting both a stress and inflammatory response leading to vascular dysfunction and predisposing to cerebrovascular events can reasonably be speculated on.[7] In this case, however, our patient presented with clinical signs which were borderline for meeting criteria for hospitalisation, indicating a more moderate course of disease. This suggests that vascular dysfunction was not the likely major mechanism leading to apoplexy, although understanding that the vascular fragility of the pituitary gland increases this risk.

During the COVID-19 pandemic, a growing number of case reports with similar clinical narratives as described in our scenario have been published. These include that of a young male with undiagnosed pituitary macroadenoma, admitted with COVID-19 PCR positive infection, and subsequent pituitary cerebrovascular accident and sadly fatality.[8] Here, central nervous system involvement of COVID-19 is postulated as a potential mechanism of endothelial dysfunction resulting in pituitary apoplexy and associated morbidity. A more recent case of a 44-year-old healthy woman with undiagnosed pituitary macroadenoma, presenting with concomitant COVID-19 infection requiring hospitalisation and pituitary apoplexy has been published.[9] Again, the authors draw on both the physical

location of COVID-19 infection giving advantage to CNS infection, as well as likely endothelial dysfunction, platelet derangement, coagulopathy and the understood fragility of the pituitary vasculature as possible explanations for this clinical scenario.

It is widely accepted that for COVID-19 to enter cells they must express both ACE-2) receptors and serine protease TMPRSS2.[10 11] Studies have shown ACE-2 receptor expression in gonadotrophs, lactotrophs, somatotrophs and corticotrophs, although in low levels, as well as TMPRSS2 pituitary expression.[12 13] This supports the possibility of direct COVID-19 infection of the pituitary, and may explain the event of pituitary apoplexy in more moderate COVID-19 illness as described in both this and other published case reports.

Patient's perspective

Following a somewhat-doubtful positive result on a COVID-19 home test, I was first taken to hospital in November 2020 (without a chance to say goodbye to my wife), stayed overnight in an open COVID-19 ward but self-discharged in the morning, arguing that I felt this was a very dangerous place as the nearest patient to me seemed to be very infectious, even in his fitful sleep. At home, I was provided with equipment to record my temperature, blood oxygen, and blood pressure and had telephone checks with my GP during the isolation period.

Towards the end of December, I again returned to hospital, this time because of a day's long splitting headache, fever and constipation, as I thought. Over a couple of day visits, investigations found I had diverticulitis, an abnormality in the heart rhythm, some issue in the lungs, a region of the brain declared 'infarcted' and a suspicion of a faulty pituitary, the last due to the insight of my GP in co-operation with the endocrinology consultant.

Another visit, at the guidance my GP, led to an admission to the hospital for several days during which I was prescribed varying levels of hydrocortisone; levothyroxine; adcal; lansoprazole; atorvastatin; and clopidogrel. I also had blood thinning injections, routine physical checks, quite a few blood tests, chest X-ray, ECG tests, an MRI scan and an eye test. I had thought I was a fairly healthy, if sleepy, individual, taking a pain-killer every now and then!

I am astounded by, but very grateful for my very thorough and still on-going examinations at this very difficult time of the pandemic, together with the unfailing courtesy shown to me by all staff, even when I was being irrational. I continue with the same medicaments and have noticed a considerable improvement mentally and physically, so am able to give my wife more support and feel energised to tackle issues I have previously ignored. I feel I have been given a new lease of life and will not forget it. Thank you.

Learning points

- Repeated admissions in well individuals often links to serious pathology.
- COVID-19 may increase the risk of pituitary apoplexy, and we should be vigilant for signs of this.
- A more insidious pathological link between COVID-19 and apoplexy may exist in addition to severe inflammatory response

Our patient presented with subtle and non-specific symptoms, which could easily have been attributed to other pathology in both primary and secondary care settings. Patients in Singapore, monitored post-COVID-19, presented with transient hypothalamic–pituitary–adrenal (HPA) axis dysfunction manifesting in hypocortisolism.[14] Additionally, ACTH production has been shown to be increased during moderate COVID-19 infection, but significantly decreased in those who were critically unwell, despite no change in GH, TSH or LH/FSH in either group.[12] It is possible that HPA axis dysfunction may contribute to symptoms attributed to 'Long COVID-19' syndrome like fatigue and memory loss.[15] Although this consequence of COVID-19 infection is likely more common than acute vascular events, an assumption about the cause of hypocortisolism in these patients may lead to a delay in diagnosis of more serious pathologies, such as apoplexy in our presented case. Therefore, a full pituitary panel performed early may help delineate between aetiologies and prevent delay of treatment.

Due to rising case reports, it seems reasonable that further research is done to elucidate any potential relationship between COVID-19 infection and apoplexy. Despite the rarity of this endocrine emergency, the prevalence of COVID-19 suggests that more patients with underlying diagnosed or undiagnosed pituitary tumours may be exposed to COVID-19. These patients may be at increased risk of pituitary dysfunction and apoplexy, and if this is the case, we as a medical profession must be conscious of this risk as symptoms such a lethargy and headache can often be attributed to viral illness alone.

Contributors KM oversaw the writing and editing of the case report, obtained the images used in the case report. S-YL was responsible for researching, planning and writing the introduction and abstract. RS was responsible for researching, planning and writing the discussion and learning points. AS was responsible for researching and writing the case summary and abstract, liaising with the patient and compiling together the sections of the report and submitting it. All authors gave final approval for submission of the case report. All authors agreed to be accountable for all aspects of the submitted case report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Albani A, Ferraù F, Angileri FF, *et al*. Multidisciplinary management of pituitary apoplexy. *Int J Endocrinol* 2016;2016:1–11.
2 Ranabir S, Baruah MP. Pituitary apoplexy. *Indian J Endocr Metab* 2011;15:188–96.
3 Oldfield EH, Merrill MJ. Apoplexy of pituitary adenomas: the perfect storm. *J Neurosurg* 2015;122:1444–9.
4 Glezer A, Bronstein MD. Pituitary apoplexy: pathophysiology, diagnosis and management. *Arch Endocrinol Metab* 2015;59:259–64.
5 Nawar RN, AbdelMannan D, Selman WR, *et al*. Analytic review: pituitary tumor apoplexy: a review. *J Intensive Care Med* 2008;23:75–90.
6 Briet C, Salenave S, Bonneville J-F, *et al*. Pituitary apoplexy. *Endocr Rev* 2015;36:622–45.
7 Biousse V, Newman NJ, Oyesiku NM. Precipitating factors in pituitary apoplexy. *J Neurol Neurosurg Psychiatry* 2001;71:542–5.
8 Solorio-Pineda S, Almendárez-Sánchez CA, Tafur-Grandett AA, *et al*. Pituitary macroadenoma apoplexy in a severe acute respiratory syndrome-coronavirus-2-positive testing: causal or casual? *Surg Neurol Int* 2020;11:304–4.
9 Ghosh R, Roy D, Roy D, *et al*. A rare case of SARS-CoV-2 infection associated with pituitary apoplexy without comorbidities. *J Endocr Soc* 2021;5:1–6.

10 Zhou P, Yang X-L, Wang X-G, *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270–3.
11 Hoffmann M, Kleine-Weber H, Schroeder S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–80.
12 Gu WT, Zhou F, Xie WQ, *et al*. A potential impact of SARS-CoV-2 on pituitary glands and pituitary neuroendocrine tumors. *Endocrine* 2021;72:340–8.
13 Stopsack KH, Mucci LA, Antonarakis ES, *et al*. TMPRSS2 and COVID-19: Serendipity or Opportunity for Intervention? *Cancer Discov* 2020;10:779–82.
14 Leow MK-S, Kwek DS-K, Ng AW-K, *et al*. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). *Clin Endocrinol* 2005;63:197–202.
15 Lazartigues E, Qadir MMF, Mauvais-Jarvis F. Endocrine significance of SARS-CoV-2's reliance on ACE2. *Endocrinology* 2020;161. doi:10.1210/endocr/bqaa108. [Epub ahead of print: 01 Sep 2020].