Pituitary apoplexy and panhypopituitarism following acute leptospirosis

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Abstract

Leptospirosis is a common tropical febrile illness which may manifest with the hepatorenal syndrome and systemic hemorrhagic manifestations. Pituitary apoplexy is a rare but life-threatening condition characterized by a hemorrhage within the pituitary gland or a pituitary adenoma. Apoplexy is very rarely associated with some inducing events such as infectious diseases such as dengue hemorrhagic fever, Hantaan virus, Puumala virus have also been reported to cause pituitary apoplexy. We present the first case of pituitary apoplexy in a patient who was being treated for leptospirosis and discuss the possible mechanisms of apoplexy in the scenario presented. We also review other reports of infectious causes that may result in pituitary apoplexy.

Keywords Pituitary adenoma · Leptospirosis infection · Pituitary apoplexy · Spontaneous adenoma resolution

Introduction

Pituitary apoplexy is a rare but life-threatening condition characterized by a hemorrhage within the pituitary gland or a pituitary adenoma. Infectious diseases such as dengue hemorrhagic fever, Hantaan virus, Puumala virus have been reported to rarely cause pituitary apoplexy. Leptospira Interrogans is the causative organism for leptospirosis, which is a common tropical febrile illness that may manifest with the hepatorenal syndrome and systemic hemorrhagic manifestations. We present the first case of pituitary apoplexy in a patient who was being treated for leptospirosis and discuss the possible mechanisms of apoplexy in the scenario presented. We also review other reports of acute pituitary apoplexy in the setting an acute infectious illness.

Case report

A 56-year-old male with a medical history of type 2 Diabetes Mellitus was admitted to a general hospital with fever, nausea, vomiting, and abdominal pain for 5 days duration. During hospital evaluation, mild hepatosplenomegaly was noted on abdominal ultrasound. His chest X-ray was unremarkable. Complete blood count (CBC) at the time of admission showed a total white blood cell count (WBC) of 11,700/microl with 90% neutrophils and 10% lymphocytes (shift to left). The erythrocyte sedimentation rate (ESR) was 62 mm/hr. The serum creatine at admission was 1.8 mg/dl and blood urea were 56 mg/dl. The platelet count was 245,000/microl. During the serological evaluation for the etiology of a febrile illness, leptospira ELISA IgM was found to be elevated. Serological investigations for other febrile illnesses including dengue, typhoid and paratyphoid were negative. A clinical diagnosis of leptospirosis with acute kidney injury was established and treatment with intravenous cefoperazone and sulbactam along with oral doxycycline was administered. Over the course of the next few days, he became afebrile and maintained adequate urine output, his WBC count decreased to 6300/microl and his serum creatinine decreased to 1.2 mg/dl. After 5 days of admission he developed sudden onset severe headache, with diplopia, and partial ptosis in the left eye. On neurological evaluation, the left
pupil was dilated and non-reactive to light. Visual field examination revealed bitemporal hemianopsia. Cerebrospinal fluid (CSF) examination was non-meningitic (CSF Glucose 85 mg/dl, protein 78 mg/dl, cells—nil). Other blood investigations included WBC 6300/microl, platelets 400,000/microl and ESR-103 mm/hr. His blood clotting time at this instance was 10 min while the bleeding time was 1 min. The estimated Prothrombin time was 13.5 Seconds (INR-1). An MRI of the brain showed a sellar mass with hemorrhagic component measuring 1.5 × 2 × 2.4 cm in size expanding the sella and extending into the suprasellar cistern. The mass showed T2W hyper intensity and TIW isointensity with hypo intense areas of “blooming” in SWI sequences, which suggested hemorrhage. Plain CT head also showed hemorrhage in the pituitary adenoma. There was Knosp grade 4 involvement of the left cavernous sinus with more than 180° encasement left Internal Carotid Artery (ICA) (Fig. 1). The MRI was consistent with apoplexy in a pituitary adenoma. On evaluation of anterior pituitary function showed evidence of hypopituitarism [S Cortisol 0.41 microgm/dl, TSH 0.16 mIU/L, Prolactin 3.21 ng/ml (1:100 dilution)]. In view of hypocortisolism, replacement doses of glucocorticoids were initiated. His hospital course was complicated by an acute kidney injury from which he made full recovery. He was then referred to our hospital for further management of the pituitary apoplexy where he was seen two weeks after the occurrence of pituitary apoplexy. On examination, the left-sided third nerve palsy had improved. There was only partial left-sided ptosis and a full range of extraocular movements were present in the left eye. Repeat visual field charting showed resolution of the prior bitemporal hemianopsia and a full visual field. The right eye examination was normal. Contrast enhanced CT scan of the head performed during this visit revealed that the adenoma has decreased in size, with resolution of the hemorrhage. We then decided to place the patient on imaging follow up. Two months later, he no longer had ptosis in the left eye,

Fig. 1 MRI Brain T1WI (A) sagittal and (B) coronal view showing isointense and (C) T2WI coronal view showing hyperintense, adenoma with left parasellar extension and encasement of left cavernous

Fig. 2 MRI Brain T1WI post contrast (A) coronal and (B) sagittal view and (C) T2WI coronal view showing small nonenhancing adenoma (arrow) on the left side of sella
the extra ocular movements were normal, and he had no visual field defects. The MRI performed during this visit showed resolution of the hemorrhagic focus and regression of the pituitary adenoma with a residual 4 mm adenoma in the left side of the Sella adjacent to the left cavernous ICA (Fig. 2). This residual lesion is being followed up with serial MRI images. He is still on replacement doses of corticosteroid and thyroid hormones and is being monitored for recovery of pituitary function.

Discussion

Leptospirosis is a zoonotic infectious disease that results in hemorrhagic diathesis, liver dysfunction, and renal failure. The causative organic L. Interrogans is a motile spiral-shaped, biflagellate that can burrow into the tissue. Rodents are the most important reservoir of the organism; however, various farm animals and wild animals may also harbor the disease. The organism is excreted in the urine of the infected host [1]. The incidence of leptospirosis in the Indian subcontinent spikes during and soon after the monsoon season, which leads to flooding of agricultural land. Human infection with Leptospira occurs through the skin, which may come in contact with water contaminated with animal urine. Drinking contaminated water may also result in infection through the mucosal surface [2]. In untreated cases, a spirochetal phase is followed by an immune phase. During this phase of spirochetemia, organisms can be found in the blood, cerebral spinal fluid (CSF), aqueous humor, and most tissues [3]. A more severe manifestation of leptospirosis is the Weil’s syndrome characterised by hepatorenal involvement, haemorrhagic and septicaemic shock [4, 5].

Studies from the subcontinent have also shown that jaundice was one of the most common symptoms of leptospirosis followed by oliguric renal failure. The diagnosis of this disease is based on assessment of clinical features and serological tests mainly the ELISA IgM estimation [3]. When leptospirosis involves the central nervous system it causes headache, nuchal rigidity, photophobia and altered sensorium in addition to other less common manifestations like seizures, delirium, encephalopathy and coma [6]. This case is unique in this regard as Leptospirosis associated with pituitary apoplexy has not yet reported.

Pituitary apoplexy is defined as clinical syndrome due to abrupt hemorrhagic and/or infarction of the pituitary gland, generally within a pituitary adenoma [7] The pituitary gland derives its blood supply from the loose capillary networks forming portal circulation supplied by superior and inferior hypophyseal arteries. A pituitary adenoma on the other hand derives its vascularity from direct arterial branches of the SHA or the IHA. This makes adenoma more susceptible to haemorrhage [7]. While uncommon, various other infections also have been reported to cause in pituitary apoplexy (Table 1). These include apoplexy caused by viral infection including Puumala [8], dengue [9], Hanta virus [10] and recently Covid-19 [11]. Tuberculosis and fungal infection associated with apoplexy have also been reported and these cases are treated with antitubercular or antifungal medication after surgery. Possible causative mechanisms that result in pituitary apoplexy in this scenario include thrombocytopenia and coagulation disorder or an autoimmune response leading to hemorrhagic vasculopathy.

With the available clinical information, we can only speculate as to the physiological mechanism that led to pituitary apoplexy, but we review various mechanisms that may result in this phenomenon. One of the proposed mechanisms of haemorrhage in leptospirosis is vasculopathy which mostly involves the capillaries. The postulated mechanism of this vascular insult is non-inflammatory vasculopathy. Disruption of endothelial cell–cell junctions, cell retraction and the consequent opening of intercellular gaps have been demonstrated by VE-cadherin immunohistochemistry [12]. Disruptions in adherens junctions due to protein alterations in VE-cadherins, p120 catenin, alpha and beta catenins has also been demonstrated [13]. This mechanism of increased permeability through cell junctions explains the occurrence of pulmonary oedema and haemorrhage in leptospirosis. Another postulated mechanism of cell surface injury in leptospirosis is the deposition of leptospiral antigen on the host cell membrane [3]. Tunjungputri et al. while investigating platelet dysfunction in leptospirosis, reported that increased VWF-platelet binding resulted in the activation and clearance of platelets leading to an increased severity of bleeding manifestations. Finally, platelet dysfunction may also be a result of uraemia, which occurs in the setting of acute kidney injury. Therefore, unlike many other viral infections like DHF, platelet dysfunction rather that an absolute decrease in platelet counts plays a greater role [14]. Hemorrhagic manifestations include epistaxis, hemoptysis, hematemesis, melena, conjunctival suffusion, skin rashes and other bleeding diatheses. Autopsy studies in have shown evidence of widespread hemorrhagic changes seen in the kidneys, liver, lungs, skeletal and cardiac muscles, serous membranes like the pleura and peritoneum and subarachnoid space [15, 16]. Panidis et al. reported a case of leptospirosis causing hypogonadism and hypopituitarism, they proposed that this could be due to direct hypothalamic pituitary axis injury by the organism or may be secondary due to release of inflammatory substance [17].

The haemorrhage that occurs within the adenoma also resolves over a period of time, some of the possible mechanisms is presence of inflammatory reaction surrounding hemorrhage which causes resorption of the blood products [18].
The time for resolution of pituitary apoplexy ranges from 6 week to 3 month [19]. Jackson et al. described 40% reduction in size at end of 1 week and 67.6% reduction at end of 7 weeks [20]. In our case it showed near complete resolution at 1 month.

**Table 1** Various infectious causes associated with pituitary apoplexy reported in literature:

| References          | Year  | Age (years) | Sex | Diagnosis     | Management of apoplexy | Outcome          | Follow up imaging | Follow up (months) | Remarks                                      |
|---------------------|-------|-------------|-----|---------------|------------------------|-----------------|------------------|-------------------|---------------------------------------------|
| Arunkumar et al.    | 2001  | 27          | M   | M. Tuberculosis| Biopsy and antitubercular medication | Improved        | Reduced size     | 9                 | Pituitary necrosis and hemorrhage. Puumala virus pituitary tissue positive for Puumala virus-N-antigen |
| Hautala et al. [8]  | 2002  | 58          | M   | Puumala       | NA                     | Death            | NA               | NA                | Steroids and thyroxine replacement          |
| Hautala et al. [8]  | 2002  | 38          | M   | Puumala       | conservative           | Recovered        | Residual tumor   | 10                | Steroids and thyroxine replacement          |
| Hautala et al. [8]  | 2002  | 19          | M   | Puumala       | conservative           | Recovered        | Residual tumor   | 2                 | Steroids and thyroxine replacement          |
| Cohen et al. [22]   | 2005  | 27          | F   | M. Tuberculosis| Surgery and antitubercular medication | Improved        | Gross total resection | 6               |                                |
| Salinas-Lara et al. [23] | 2006 | 42          | F   | Mucormycosis  | Surgery                | Death            | NA               | NA                |                                |
| Kumar et al. [24]   | 2011  | 31          | F   | Dengue        | Surgery                | Improvement in visual fields | NA     | 3                 |                                |
| Wildemberg et al. [25] | 2012 | 40          | M   | Dengue        | Surgery                | Improved         | NA               | 3                 |                                |
| Wildemberg et al. [25] | 2012 | 38          | M   | Dengue        | Surgery                | Improved         | NA               | 2                 |                                |
| Panigrahi et al. [26] | 2014 | 43          | M   | Dengue        | Surgery                | Improvement in visual fields | Near-total resection | 3           |                                |
| Seng Kiong Tan et al. [9] | 2014 | 53          | M   | Dengue        | Surgery                | Residual vision defect present in the right eye | Residual present | 3                 |                                |
| Ayturk et al. [10]  | 2015  | 62          | M   | Hantavirus    | Surgery                | Recovered        | NA               | 12                | Amp B and voriconazole for aspergillosis Pulmonary complications Full-term delivery prior to pituitary surgery |
| Kinberg et al. [27] | 2018  | 67          | F   | Aspergillosis | Conservative           | Recovered        | Residual tumor in the cavernous sinus | 6                 |                                |
| Pineda et al. [28]  | 2020  | 27          | M   | SARS-CoV-2    | Conservative           | Death            | NA               | NA                |                                |
| Chan et al. [11]    | 2020  | 28          | F   | SARS-CoV-2    | Surgery                | Improved         | NA               | NA                |                                |
| Catarino et al. [29] | 2020  | 55          | F   | Septate fungal infection (species not described) | Surgery and antifungal medication | Improved clinically | Gross total resection | 4               |                                |

**Conclusion**

Leptospirosis is a common tropical febrile illness that may manifest with the hepatorenal syndrome and systemic hemorrhagic manifestations. Leptospirosis leads to a non-inflammatory vasculopathy affecting capillaries.
disrupting endothelial cell–cell junctions. Very rarely, in a patient harboring a pituitary adenoma this vasculopathy may result in pituitary apoplexy.

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