Review article

Pituitary dysfunction in infective brain diseases

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ABSTRACT

Infectious diseases of the central nervous system (CNS) are increasingly being recognized as important causes of hypopituitarism. Although tuberculosis is the most common agent involved, non-mycobacterial agents like viruses, bacteria, fungus, and protozoa are important causes in our country. Involvement post infections could be due to a strategically located tuberculoma, or pituitary abscess, or meningoencephalitis. Although it might not be reasonable to screen all patients with CNS infections for hypopituitarism, awareness of the possibility and clinical follow-up for suggestive symptoms is required.

Key words: Pituitary, infections, hypopituitarism

Hypothalamic-pituitary insufficiency (HPI) can be caused by diverse etiologies. The important causes of hypopituitarism are pituitary tumors (including craniopharyngioma), postoperative and post-radiotherapy states, vascular conditions, snake bite, head injury, and autoimmune diseases such as hypophysitis. Of late, infectious/inflammatory conditions are increasingly being recognized as important causes as well. The infectious agents that can cause HPI are *Mycobacterium tuberculosis* and non-mycobacterial agents such as bacteria, fungi, spirochetes, viruses, and protozoa.

The most common infectious agent affecting the hypothalamic pituitary axis is *Mycobacterium tuberculosis*.[1]

Various studies have been done to assess the hypothalamic pituitary axis in the acute phase of the illness as well as after recovery. Hypothalamopituitary dysfunction due to tuberculosis can be due to the presence of a strategically placed tuberculoma, vasculitis, or exudates around the sellar region. Tubercle bacilli are believed to reach the pituitary by hematogenous spread from extracranial sources or from the extension of infected skull bones.[2-4] Dhanwal *et al.*, conducted a prospective study on 75 untreated adult patients with tuberculous meningitis (TBM) to evaluate hypothalamic pituitary abnormalities in newly diagnosed patients. Thirty-two (42.7%) cases showed relative or absolute cortisol insufficiency. Twenty-three (30.7%) cases showed central hypothyroidism and 37 (49.3%) cases had hyperprolactinemia. No patient had evidence of diabetes insipidus (DI). Multiple pituitary hormone deficiency was seen in 22 (29.3%) cases.[5] While tubercular abscess of the brain has been reported, primary tubercular abscess of the pituitary is extremely rare. The literature review yields only few cases of primary tubercular lesion of the pituitary and the diagnosis was reached only after surgery. About 30-50% of patients with pituitary tubercular abscess/tuberculoma may have anterior pituitary hormone deficiencies or central DI at the onset. The earliest manifestation is growth hormone (GH) deficiency, followed by gonadotropin (luteinizing hormone (LH)/follicle stimulating hormone (FSH)) and adrenocorticotropic hormone (ACTH) deficiency.[6] However, in cases with tuberculoma of the pituitary gland, the most frequent deficiencies encountered are ACTH, thyroid stimulating hormone (TSH), and hyperprolactinemia.[7,8]

Primary pituitary abscesses of various etiologies are encountered in tropical medicine and pituitary abscess must be considered in the differential diagnosis of a parasellar mass. They usually occur in immunocompromised subjects, and are caused by Aspergillus, Nocardia, *Candida albicans*, or

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Pneumocystis jeroveci. The endocrine manifestations include DI, hyperprolactinemia, and gonadal dysfunction.[9] The posterior pituitary is more often involved because it receives its blood supply directly from the systemic circulation via the internal carotid arteries. At times, these infections, including tuberculosis, may lead to central precocious puberty.[10] This may occur because of increased intracranial pressure, which activates the hypothalamic-pituitary-gonadal axis, or because of irritation of the basal hypothalamus. We have come across a case of isosexual precocity in a 6-year-old girl due to hypothalamic tuberculoma, diagnosed with stereotactic needle biopsy. In the largest series of pituitary abscess published till date, the authors report that abscess can be successfully treated, but the accompanying hypopituitarism is usually irreversible.[11]

Non-mycobacterial acute central nervous system (CNS) infections are a relatively rare cause of hypopituitarism and have been published as isolated case reports and few retrospective studies. Most of these cases have been reported following viral meningoencephalitis. The earliest such case reports came from Hägg *et al*., who reported two cases of persistent HPI following acute viral meningoencephalitis due to Coxsackie B5 virus.[12] Subsequently, Kupari *et al*., reported HPI following influenza A and herpes simplex meningoencephalitis.[13] Isolated posterior pituitary insufficiency has also been described especially in children. In this retrospective analysis, severe CNS infection was associated with central DI in eight out of 73. The infectious agents were group B streptococcus, *Hemophilus influenzae*, *Streptococcus pneumoniae*, and unknown virus.[14] Central DI has also been reported in adults with acute CNS infections, but in association with multiple pituitary hormone deficiency.[15] Involvement of the hypothalamus with a viral destruction of vasopressin producing neurons seems to be the cause of central DI. In almost all reported cases, the anterior pituitary insufficiency was caused by viruses and only one bacterial meningoencephalitis associated with DI and suspected corticotropic insufficiency has been reported. A prospective study by Tsiakalos *et al*., was done to investigate pituitary function in 11 patients admitted with infectious meningitis during the acute phase and after 12 months. During the acute phase, five patients (31.25%) showed apparent pituitary hormone deficiencies: Two with gonadotroph and three with somatotroph deficiency. The exact status of corticosteroid sufficiency could not be defined in four patients, because no dynamic test was performed in the acute phase. In addition, seven patients (44%) had probable low triiodothyronine (T3) syndrome. At 12 months, five patients (31.25%), two with viral and three with bacterial meningitis, had at least one anterior pituitary hormone deficiency; two had isolated corticotropic; and one isolated somatotropic deficiency. Combined corticotropic and somatotropic deficiencies were detected in two. New-onset deficiencies accounted for four of those five patients, whereas one demonstrated persisting somatotropic deficiency. All cases of low T3 syndrome resolved at 12 months.[16] In a recent retrospective study by Schaefer *et al*., pituitary function testing was performed in 19 patients with previous neuroborreliosis, encephalitis, or meningitis following an interval of between 10 and 56 months after the acute event and it was found that hypothalamic pituitary dysfunction, especially isolated corticotrophin insufficiency, developed in 21% patients and borderline hypogonadotropic hypogonadism was seen in two (11%). None had somatotroph or thyrotroph deficiency or central DI.[17] Our recent experience with a case of multiple pituitary hormone deficiency due to racemose neurocysticercosis involving the pituitary has been published.[18]

Unrecognized selective or panhypopituitarism as a part of a critical illness is associated with worse overall prognosis, increased risk of severe infectious complications, and reduced survival. Dhanwal *et al*., studied 30 untreated adult patients with acute meningitis, meningoencephalitis or encephalitis, due to various non-mycobacterial agents (acute pyogenic meningitis (n = 23), viral meningoencephalitis (n = 4), brain abscess (n = 2), and cryptococcal meningitis). Adrenal insufficiency both absolute and relative was seen in seven (23.3%) and hyperprolactinemia was seen in nine (30.0%). One had central hypothyroidism and seven (23.3) showed low levels of LH and/or FSH. None of the patients showed had central DI.[1]

A recent study was conducted on 16 patients with acute infectious meningitis to investigate whether autoimmune mechanisms could play a role in the pathogenesis of acute meningitis-induced hypopituitarism and the patients were evaluated in the acute phase, and at 6 and 12 months after the acute meningitis. In the acute phase, 18.7% of the patients had GH deficiency and 12.5% had ACTH and FSH/LH deficiencies. At 12 months after acute meningitis, 6/14 (42.8%) had GH deficiency, 1/14 (7.1%) had ACTH, FSH, and LH deficiencies, 2/14 (14.3%) had combined hormone deficiencies, and 4/14 (28.6%) had isolated hormone deficiencies at 12 months. Four of nine (44.4%) of hormone deficiencies at 6 months were recovered at 12 months, and three of eight (37.5%) hormone deficiencies at 12 months were new-onset hormone deficiencies. The frequency of antihypothalamus antibodies (AHAs) and antipituitary antibodies (APA) positivity was substantially high, ranging from 35 to 50% of the patients throughout the 12 months period. However, there were no significant correlations between AHA or APA positivity and hypopituitarism. Further long-term

prospective investigations need to be carried out on a larger cohort of patients to understand the role of autoimmunity in the pathogenesis of late hypopituitarism after acute infectious meningitis.[19]

Pituitary dysfunction with overt clinical symptoms is not a frequent consequence of acute meningitis in children and invasive assessments should be reserved for selected cases where there is slow growth or other clinical suspicion of hypopituitarism.[20]

Human immunodeficiency virus (HIV) infection is a common cause of pituitary endocrinopathy in the tropical setting. Pituitary infection by *Toxoplasma gondii* and cytomegalovirus (CMV) have been documented in patients with HIV.[21] It is postulated that HIV infection triggers macrophages to secrete interleukins (IL-1) and tumor necrosis factor (TNF). IL-1 produced in the median eminence can also affect hypothalamus and pituitary. Increased release of CRH from the hypothalamus may cause increase in ACTH secretion reported in early HIV disease.[22-24] However, IL-1 has been found to directly stimulate cultured pituitary cells to secrete ACTH. Idiopathic adenohypophyseal necrosis observed in 10% HIV-infected patients at autopsy is thought to be due to direct effect of HIV. Increased prolactin levels and gynecomastia have been demonstrated among these patients. More than 20% of HIV-infected men with stable disease were reported having hyperprolactinemia and this was significantly associated with opioid use and increased CD4 count but not with antiretroviral therapy.[25] HIV infection reduces dopaminergic tone and thereby increases the bioactivity of prolactin, though the mechanism of this effect remains unclear.[26] Viscerally obese HIV-infected patients with lipodystrophy show GH deficient state with decreased amplitude of mean overnight GH level and GH pulse, likely due to increased somatostatin tone, decreased ghrelin, and increased circulatory free fatty acid due to enhanced lipolysis.[27]

In conclusion, HPI following CNS infections is an important clinical entity, especially in the tropics, and a high index of clinical suspicion is required to identify this condition both in the acute settings and in the long-term follow-up of patients. Further studies should focus on the impact of HPI and its early recognition and treatment in the mortality and morbidity of CNS infections.

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