Hypophysitis

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KEYWORDS

• Hypophysitis • Autoimmune • CTLA-4 • IgG4 • Hypopituitarism • Diabetes insipidus

KEY POINTS

- Hypophysitis can be classified according to anatomic, histopathologic, and causal criteria.
- Epidemiologic distribution differs according to anatomic classification.
- New categories of this disease have recently been established, such as IgG4-related hypophysitis and secondary hypophysitis caused by anticytotoxic T-lymphocyte antigen-4 antibodies.
- Clinical features can be divided into 4 categories: sellar mass effects, hypopituitarism, central diabetes insipidus, and hyperprolactinemia.
- Clinical management of hypophysitis includes pituitary mass reduction and hormone replacement therapy.

INTRODUCTION

Hypophysitis is characterized by lymphocytic infiltration of the pituitary gland. Depending on the anatomic location of the infiltrate, hypophysitis is classified as lymphocytic adenohypophysitis (LAH), lymphocytic infundibuloneurohypophysitis (LINH), or lymphocytic panhypophysitis (LPH).[1–3] Based on the histopathologic features, there are 2 main forms of hypophysitis (lymphocytic or granulomatous hypophysitis) and 3 rare variants (xanthomatous, IgG4-related, and necrotizing hypophysitis) (**Box 1**).[1,4–7] This rare infiltration of the pituitary grand occurs mostly in its primary form. However, secondary hypophysitis, presenting as pituitary inflammation, can occur as a symptom of causes such as sellar diseases, systemic diseases, or drugs such as anticytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies, which have recently been approved for cancer immunotherapy.[1,8] Hypophysitis is also associated with other autoimmune diseases such as Hashimoto thyroiditis, autoimmune polyglandular syndrome (APS), Graves disease, systemic lupus erythematosus, Sjögren syndrome, and type 1 diabetes, reflecting its autoimmune pathogenesis.[1]

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Box 1
Classification of primary hypophysitis

1. Anatomic classification
    - Lymphocytic adrenohypophysitis (LAH)
    - Lymphocytic infundibuloneurohypophysitis (LINH)
    - Lymphocytic panhypophysitis (LPH)
2. Histopathologic classification
    - Lymphocytic hypophysitis
    - Granulomatous hypophysitis
    - Xanthomatous hypophysitis
    - IgG4-related hypophysitis
    - Necrotizing hypophysitis
    - Mixed forms

EPIDEMIOLOGY

The prevalence and incidence of primary hypophysitis have been estimated mainly from data on surgeries conducted on patients with a pituitary mass or on autoptical specimens. The prevalence of hypophysitis is approximately 0.24% to 0.88%,[1,5,9] and the annual incidence is approximately 1 in 9 million, although this value may be an underestimation.[10] Based on histopathologic classification, the most common form of this disease is lymphocytic hypophysitis (LH; 71.8%), followed by granulomatous hypophysitis (18.6%) and xanthomatous hypophysitis (3.3%), whereas IgG4-related and necrotizing hypophysitis are rare.[5] However, the prevalence of IgG4-related hypophysitis may be underestimated and needs to be clarified.[11] Further characterization is also required for this new entity of hypophysitis, which will improve the definition of the disease.

Hypophysitis generally occurs in the fourth decade of life and is rare in children and the elderly.[12] LAH is 4.3 to 6 times more common in women, especially during late pregnancy and the postpartum period; LINH affects both genders equally, and LPH is more frequent in men (1.8:1).[9,12] The mean age of onset for LAH is lower, particularly in women (women: 35 $\pm$ 13 years; men: 45 $\pm$ 14 years), than that for other forms (42 $\pm$ 17 years).[1] Furthermore, the onset of LPH occurs earlier than that of LINH,[2] and it was even shown to occur at less than 15 years of age for 4 of 34 patients (12%) in 1 study.[2]

RISK FACTORS

Well-known risk factors for primary hypophysitis are pregnancy or childbirth. LAH commonly presents between the last month of gestation and the first 2 months of the postpartum period (57%–69%).[1,12] An additional risk factor for LAH is aseptic meningitis.[13] Several risk factors for secondary forms of hypophysitis have also been identified; these are summarized in **Box 2**.

PATHOPHYSIOLOGY

Table 1 summarizes the pathologic features of hypophysitis.[4,6,11,12,14,15] Antipituitary antibody (APA) is approved for clinical use in indirect immunofluorescence. Patient