Autoimmune pituitary inflammation

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Abstract: Autoimmune Hypophysitis (AH) is often referred in the literature as lymphocytic pituitary inflammation. It is the most common form of rare, chronic inflammation states affecting this gland. In most cases it has autoimmune character. Symptoms of pituitary inflammation are mostly headaches, dysfunction of anterior and/or posterior pituitary lobe and visual disturbances. Diagnostics is extremely difficult and inflammation itself is probably diagnosed too rare. Autoimmune Hypophysitis coexist with other autoimmune endocrinopathies. The golden standard in Autoimmune Hypophysitis diagnosis is biopsy and magnetic resonance imaging (MRI) is also used. In relation to rare occurrence of the Autoimmune Hypophysitis, varied clinical picture and lack of standardized research on large group of patients there are no described standards of conduct with those patients.

Introduction:
Hypophysitis is a rare occurring disease diagnosed in less then 1 in over 9 million cases every year(1,2). It can be primary or secondary in relation to local process or systemic process. In most cases it has autoimmune character, but other causes include secondary inflammation to tumo ur or cyst on the sella turcica, systemic diseases, infections or drug induced causes(3). Symptoms of pituitary inflammation are mostly headaches, dysfunction of anterior and/or posterior pituitary lobe and enlargement of pituitary and/or pituitary peduncle stated in imaging examination(3,4).
Diagnostics of this condition is extremely difficult and inflammation itself is probably diagnosed too rare(1-3). Differential diagnosis is wide and multifaceted, including primary cancer, metastasis and lymphoproliferative diseases(1-3).

At the beginning of twentieth century appeared first histological descriptions noticing lymphocytic inflammation of the gland. Autoimmune basis of this condition was confirmed in 1950’s. Since then, medical knowledge in this area was expanded in many researches.

**Purpose of work:**
Presentation of the topic of Autoimmune pituitary inflammation, analysis of current state of knowledge and propositions about possible methods of treatment.

**Description of current state of knowledge about the topic:**
Autoimmune Hypophysitis (AH) is often refereed in the literature as lymphocytic pituitary inflammation. It is the most common form of rare, chronic inflammation states affecting this gland(5-7). Autoimmune Hypophysitis is observed mostly in Caucasian population. It occurs more often in women then men and it is correlated to pregnancy. Average age in the moment of diagnosis is 34,5 years old among women and 44,7 years old among men(5,8). [Table 1]

| Table 1. General characteristics of Autoimmune Hypophysitis (AH) (F – female, M – male) (8) |
|----------------------------------------------------------|
| SEX – F:M = 8:1                                          |
| Age in moment of diagnosis (years) – F 34,5; M 44,7       |
| Race – Caucasian: Japanese = 3:1                         |
| Correlation with pregnancy – often occurring 6 months before and 6 months after the birth |
| Genotype – HLA DR4 (44%), HLA DR5 (23%)                 |
| Other autoimmune disease is present                      |
| Occurring of other autoimmune disease among patient’s family |

Clinical image of Autoimmune Hypophysitis varies individually. There are four categories of symptoms occurring in cycle of remission and relapse. The earliest and most common are headaches and visual disturbances. They are the result of pressure of enlarging pituitary gland on the surrounding structures of the brain. Second category of symptoms is associated with deficiency of hormones which are produced by anterior lobe of pituitary gland. The most common is deficiency of Corticotropin (ACTH) and also: Thyroid Stimulating Hormone (TSH), Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin (PRL), Growth Hormone (GH). Third category are the symptoms of diabetes insipidus – polydipsia and polyuria, caused by damage of posterior lobe of pituitary gland. Least often are symptoms of hyperprolactinaemia in form of menstrual disorders, potency disorders and galactorrhea(5-8).

The knowledge about pathogenesis, frequency of occurrence and natural course of the condition is mostly unconfirmed according to the principles of good clinical practice and evidence-based medicine. Due to growing doctor’s awareness, development of diagnostic, non-invasive imaging of pituitary gland and transsphenoidal surgery as well as use of animal’s models in research, the knowledge is expanding and disease itself is diagnosed more often. The best conformation of this fact are growing numbers of AH’s descriptions in literature(5-9).
Defining pathological characteristic of Autoimmune Hypophysitis is lymphocytic inflammatory infiltration. Usually it covers whole gland, deforming it's natural structure and causes impairment of function. Besides lymphocytes, the other inflammatory cells are present and they can play a major role in immunopathology. Most authors suggest the autoimmune character of the disease, but the viral etiology is also considered. Immunohistochemical research shows presence of polyclonal lymphocytes T and B, without dominant type of lymphocytes which is typical for autoimmune diseases (6,10).

Other evidences suggesting autoimmune basis of Autoimmune Hypophysitis include improvement of patient’s condition in response to treatment with immunosuppressants – mostly glicocorticosteroids, but also metotrexate or azathioprine. Presence of Antipituitary Antibodies (APA) and coexistence with other diseases with proven autoimmune nature (5-8,11).

Moreover, other autoimmune diseases are frequently found in the families of Autoimmune Hypophysitis patients. Probably it has connection with genetic predisposition and presence of HLA-DR4 and HLA-DR5 alleles. [Table 2] (6,10)

| Criteria                                                                 | Presence in AH |
|--------------------------------------------------------------------------|----------------|
| Lymphocytic infiltration of target organ                                 | Yes            |
| Characteristic image in CT and MRI suggesting Lymphocytic infiltration of target organ | Yes            |
| Evidence of disease induction among experimental animals                 | Yes            |
| Presence of autoantibodies directed against target organ                 | Yes            |
| Identification of specific autoantibodies                                | Debatable      |
| Coexistence with other autoimmune diseases and/or in presence of other specific autoantibodies | Yes            |
| Cycles of remission and relapse                                          | Yes            |
| Good respond to immunosuppressive treatment                              | Yes            |

According to the literature, in over 20% of cases Autoimmune Hypophysitis coexist with other autoimmune endocrinopathies such as: Autoimmune Thyroid Diseases (AITD), Hashimoto’s Thyroiditis (HT) –7,4%, Graves’ Disease (GB) – 1,6%, Polyglandular Autoimmune Syndrome type II (PAS II)- 1,8%, Diabetes Mellitus Type 1 (DM1)- 0,8% and Addison's disease (AD)- 0,5%.

This research was conducted among adult population and there is lack of data for pediatric population. Among patients with organ-specific and non specific autoimmune diseases marks of Antipituitary Antibodies can be used in order to diagnose patients, who may develop autoimmune pituitary inflammation. (5-7, 11, 12)

The specific autoantibody against which the autoimmune response is developing was not identified untill this day. The role of alpha-enolase is raised, considering it’s coexpression in placenta, which could be the explanation for strong relation of the disease to pregnancy. (13) Antibodies that are recognising alpha-enolase are described in many other diseases, such as endometriosis, lupus erythematosus and Wegener's granulomatosis. (5) As in the case of others
endocrine glands, autoantibodies of the pituitary gland are mainly lipoproteins, located in intracellular membrane of endoplasmic reticulum. (8)
The golden standard in Autoimmune Hypophysitis diagnosis is biopsy. Because of the invasive nature of this procedure, patients often do not give consent to this. In diagnostics of Autoimmune Hypophysitis magnetic resonance imaging (MRI) is also used, in order to differentiate this disease to pituitary tumor. (2)

Summary:
In relation to rare occurrence of the Autoimmune Hypophysitis, varied clinical picture and lack of standardized research on large group of patients there are no described standards of conduct with those patients. We can highlight various strategies applied together or separated, depending on patient’s symptoms: wait-and-see attitude together with observation in case of patients without clinical symptoms, hormonal replacement therapy in case of patients with hypopituitarism or therapy with dopaminergic drugs in case of patients with hyperprolactinaemia. Conservative therapy with glicocorticosteroids and in recent years also with other immunosuppressants such as metotrexate or azathioprine, in order to reduce the size of the gland, is considered as controversial. Surgical treatment in case of pressure symptoms is performed via sphenoid sinus. In case of ineffectiveness of above methods radiotherapy may also be used. (4,8,14).

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