The Immune Response in Primary- and Immunotherapy-Induced Hypophysitis

Subjects: Allergy

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Hypophysitis is a rare and potentially life-threatening disease, characterized by an elevated risk of complications, such as the occurrence of acute central hypoadrenalism, persistent hypopituitarism, or the extension of the inflammatory process to the neighboring neurological structures. In recent years, a large number of cases has been described. The diagnosis of hypophysitis is complex because it is based on clinical and radiological criteria. Due to this, the integration of molecular and genetic biomarkers can help physicians in the diagnosis of hypophysitis and play a role in predicting disease outcome.

Keywords: Hypophysitis

1. Antibodies in Primary Autoimmune Hypophysitis

Several studies were conducted on the anti-pituitary antibodies (APA). APAs have been recognized for several years as the only molecular biomarkers for hypophysitis and were investigated with different techniques, such as the complement consumption test, immunoblotting with homogenate of human autopsy pituitaries, radioligand binding assays, and immunofluorescence [1][2]. Over the years, several attempts were made to optimize the immunofluorescence method, specifically to identify the best substrate. Experiments were conducted with pituitary slides from several animals: rats, rabbits, mice, baboons, and, eventually, humans [3]. The baboon pituitary was considered the best substrate for APA identification. The serum APAs bind to the corresponding antigens present on the pituitary sections. The antigen-antibody complexes are detected by means of a goat anti-human IgG conjugated with a fluorescein isothiocyanate (FITC) [4]. IgG FITC was adsorbed with monkey serum to remove non-specific fluorescence [4]. The sera of patients were considered positive for a APAs starting at the dilution rate of 1:8 [4]. The samples were considered positive in cases with a diffuse immunofluorescence pattern and an intracytoplasmic staining in the majority of the fields. In each assay, a positive and negative control needs to be included [4]. The clinical relevance of APAs has been keenly discussed in previous research and APAs were widely considered a pathogenic marker of hypophysitis rather than a diagnostic tool. In fact, APAs were reported in other autoimmune disorders of the pituitary gland or in autoimmune systemic diseases, such as Sheehan's syndrome, idiopathic growth hormone (GH) deficiency, idiopathic hyperprolactinemia, idiopathic hypopituitarism, brain traumatic injury, autoimmune polyendocrine syndromes and empty sella syndrome, but also in patients with pituitary adenomas or in healthy individuals [2][5][6]. The experimental hypophysitis of SJL/J models showed that APAs may be detected with a higher concentration in the initial days after mouse immunization and gradually reduce thereafter [7]. For these reasons, the APAs were also considered clinically helpful for the diagnosis of acute hypophysitis in humans, but only if detected at a high concentration [5]. Recently, we proved that APAs are more prevalent in patients affected by PAH (68.4%) than in patients affected by not-secreting pituitary adenomas (22%) and in health controls (14%) [8]. In the same study, we found that positivity for anti-pituitary and anti-hypothalamus antibodies was simultaneously detected in 52.9% of patients affected by PAH and in no patients carrying a non-secreting pituitary adenoma. As a consequence, although the presence of APAs may not exclude a non-secreting pituitary adenoma, the simultaneous positivity for anti-pituitary and anti-hypothalamus antibodies makes a diagnosis of not-secreting pituitary adenomas unlikely, with an odds ratio of 0.27 (95%IC: 0.13–0.57) [8]. In addition, the detection of APAs positively predicts the outcome of treatment with glucocorticoids in PAH [9].

2. Putative Antigens of Primary Autoimmune Hypophysitis

Several studies focused on identifying the auto-antigens of PAHs. Lupi et al. [7] demonstrated, through their SJL/J experimental model, that the extracts of whole mouse pituitaries and cytosol fractions had the strongest immunogenic proprieties, with respect to pituitary membranes and nuclei, and that a high immunogen dose is associated with more severe hypophysitis [7]. The immunoblotting of pituitary cytosol proteins and patients' sera allowed the identification of a

49-kilo Dalton and a 40-kilo Dalton protein respectively in 70% and in 50% of histologically-proven hypophysitis [10]. A subsequent study recognized the 49-kilo Dalton protein as the alpha-enolase [1], which acts as a glycolysis enzyme, a plasminogen receptor, and a controller of cell growth and differentiation, through the downregulation of *c-myc* proto-oncogene expression [11]. Anti-alpha enolase antibodies were detected in other autoimmune diseases, such as mixed cryoglobulinemia, arthritis with kidney involvement, discoid and systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, vasculitis with positive anti-neutrophil cytoplasmic antibodies, primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, inflammatory bowel disease, and primary membranous nephropathy [1]. The antibodies anti-GH, anti-pituitary gland specific factor 1a (PGSF1a) and 2 (PGSF2), anti-chorionic somatomammotropin hormone, anti-prohormone convertase, anti-pituitary-specific positive transcription factor 1 (PIT-1), anti-pro-opiomelanocortin (POMC), anti-alpha rad guanine nucleotide dissociation inhibitor (GDI), anti-secretogranin, anti-tudor domain-containing protein (TDRD6) and anti-T-PIT were detected in patients affected by hypophysitis and by hypopituitarism [11][12][13][14][15][16][17][18]. Growth hormone and proopiomelanocortin were also suggested as antigens of IgG4-related hypophysitis [14]. Antibodies against GH, PGSF1a, PGSF2, and T-PIT were also detected in healthy controls and in patients affected by isolated adrenocorticotropic hormone (ACTH) deficit or by other autoimmune diseases [11][12]. Finally, rabphilin-3A was described as a putative antigen of infundibulo-neuro-hypophysitis [19][20].

This different antigenic profile in infundibulo-neuro-hypophysitis may be explained further by the different histological characterization of the adeno-pituitary (which t is composed of epithelial tissue) and of the neuro-pituitary (which is composed of neural tissue). This dual nature of the gland may be due to its embryogenesis. During uterine development, a caudal extension of the primitive forebrain (the diencephalon) grows towards the roof of the primitive oral cavity. Adenohypophysis derives from epithelial cells (the oral ectoderm) and is composed of the pars distalis, a thin layer called the pars tuberalis, and the pars intermedia, which is lost in adult humans. The neurohypophysis develops from a downgrowth of neural tissue at the base of the diencephalon (corresponding to the hypothalamus in the adult) and gives rise to the pars nervosa, the infundibulum, and the median eminence. The infundibulum and the pars tuberalis make up the pituitary stalk [21]. This different embryogenic origin of the adeno-pituitary and the neuro-pituitary may also explain the different inflammatory involvement that occurs in adeno-hypophysitis, infundibulo-neuro-hypophysitis, and pan-hypophysitis. In fact, the inflammatory process involves only the adeno-pituitary in adeno-hypophysitis. It involves the pituitary stalk and the neuro-pituitary in cases of infundibulo-neuro-hypophysitis, and it involves all these structures in cases of pan-hypophysitis [22].

3. Cell-Mediated Immune Response in Primary Autoimmune Hypophysitis

Few studies have been conducted to investigate the cell-mediated immune response in PAHs. The flow cytometric analysis of experimental hypophysitis conducted on the SIL/J murine models showed that the number of hematopoietic cells increased in immunized mice as compared to not-immunized mice [7]. In fact, the hematopoietic cells accounted for about 85% of all the cells of pituitary extracts in the SIL/J mice and only 2% of the cells of the not-immunized mice The lymphocytes were the most prevalent hematopoietic cells, with CD4-positive T-lymphocytes three times more abundant than CD8-positive T-lymphocytes [7]. The majority of the T-lymphocytes expressed CD44, suggesting an activated/memory phenotype. Furthermore, monocytes/macrophages and granulocytes were detected in SIL/J experimental hypophysitis [7]. In particular, the dendritic CD11-positive cells were identified in close proximity to the lymphocytes aggregate, suggesting that dendritic cells present antigens to infiltrating T-cells, inducing the activation of T-cells and stimulating the secretion of cytokines. The gamma-interferon and the 17 interleukin were detected through cytokine array membranes on pituitary extracts of SIL/J hypophysitis [23]. Moreover, immunohistochemical studies proved the presence of double PCNA/CD3-positive and double PCNA/B220-positive lymphocytes, suggesting that the active T and B-cells proliferated into the pituitary gland [23]. In fact, PCNA is a marker of cell proliferation. This data was also confirmed in a single case report of a female patient with PAH, with a pituitary infiltration of double CD3/Ki67- and double CD20/Ki67-positive lymphocytes [23].

4. The Genetics of Primary Autoimmune Hypophysitis

Currently, the genetics of hypophysitis are an open issue. The identification of genetic markers for this disease is difficult due to the complex etiology of this disorder and the possible coexistence of other causes of hypopituitarism, such as congenital diseases that lead to an abnormal development of the pituitary gland, as observed in patients who carried the mutations in the *PIT1* or *PROP1* genes [24][25].

Child-onset hypopituitarism is often due to genetic disorders and its identification should take into account the differential diagnosis from pediatric hypophysitis and, more frequently, from pituitary hyperplasia. On the other hand, there are relevant data about the genetic components underlying autoimmune disorders. In PAH, the same HLA polymorphisms were described.

Beressi et al. [26] reviewed 17 PAH cases that featured the HLA genotype from 1987 to 1999 and described the presence of HLA-DR4 in 44% of cases and of HLA-DR5 in 23% of cases. Instead, more recently, in a series of 15 PAH patients, the HLA haplotypes DQ8 and DR53 were identified, respectively, in 87% and 80% of cases [27].

5. Molecular Mechanisms in Immunotherapy Induced Hypophysitis

Hypophysitis is a clinically significant endocrine toxicity in patients receiving treatment with immune check-point inhibitors (ICIs), such as monoclonal antibodies (mAbs), against the cytotoxic T-lymphocyte antigen 4 (CTLA4) and programmed cell death-1 (PD-1) [28]. However, few data and evidence are provided on the molecular mechanism of this disorder.

CTLA-4 is expressed on the cell surface of active CD4-positive and CD8-positive T-cells and binds the CD80 and CD86 that are expressed on the cell surface of antigen-presenting cells (APCs), with higher affinity and avidity than CD28 [29]. The engagement of CTLA-4 with CD80 and with CD86 mitigates the immune response [30]. The primary activity of the CTLA-4 pathway is the draining of the lymph nodes, where naïve T-cells are primed by exposure to tumor antigens (presented by APCs) and become activated [31]. The mAbs act through the inhibition of the CTLA-4 pathway, with a subsequent over-activation of T-lymphocytes that may predispose to the onset of autoimmune disease, as IIH.

Similarly, PD-1 acts as a second inhibitory receptor and is expressed mainly on activated CD8-positive T-lymphocytes [32]. PD-1 is triggered by PD-ligands 1 and 2 (PD-L1 and PD-L2, respectively), which constitutively reside on tumor cells [33][34]. The sites of activation of the PD-1 pathway are the peripheral tumoral tissues and the tumor microenvironment (TME) [31]. The binding of PD-1/PD-L1 suppresses the activity of T-cells [35], converts T-helpers into T-regulatory cells [36] and activates pro-survival signaling pathways in cancer cells through a mechanism of resistance to cytotoxic T-lymphocytes [37]. Treatment with mAbs anti-PD-1 and with anti-PD1L is associated with a high frequency of autoimmune disorders, also involving endocrine toxicity [28].

The genetic polymorphisms of the *CTLA-4* and of *PD-1* genes can increase the incidence of autoimmune disease, including IIH [38][39]. Many of these polymorphisms do not actually change the CTLA-4 amino acid sequence, but can modify the affinity for the CTLA-4 mAb, increasing the risk of occurrence of immunotherapy-induced autoimmune disorders [38]. In the diagnostic work-up, there is no recommendation to investigate the *CTLA-4* gene polymorphisms. Among the genetic mechanisms behind the IIH, this mechanism should also be taken into consideration.

Cases of isolated ACTH deficiencies are also observed during immunotherapy, in the absence of the typical radiological features of hypophysitis. Isolated ACTH deficiencies are mainly classified as congenital or acquired. In congenital forms, the two most commonly involved genes are the *T-PIT* gene (better known as the TBX19 gene) and the *POMC* gene (the *melanocortin* gene) [40]. According to more recent research, IIH and ACTH deficits may be considered two different endocrine toxicities. In a recent study, conducted on 62 cancer patients treated with ICIs, the prevalence of APAs was similar among the five patients who developed an IIH (APA positivity: 80%) and in those who developed an ACTH deficit (APA positivity: 88.2%) [41]. Moreover, Kanie at al. [42] recently described two patients who developed anti-ACTH antibodies and central hypoadrenalism during ICI therapy. The authors observed ACTH expression on the tumor cell surface of a kidney neoplasia and of a melanoma, and suggested that the ectopic expression of cancer cells in ACTH can promote the immune response with the synthesis of anti-ACTH antibodies that can also act on the pituitary corticotroph cells, inducing central hypoadrenalism. In this view, the ACTH deficit may be considered as a paraneoplastic syndrome.

Some studies also investigated HLA haplotypes in patients affected by IIH and immunotherapy-induced hypopituitarism, showing that the prevalence of HLA-Cw12 and HLA-DR15 was significantly higher in patients with immunotherapy-induced hypophysitis. Instead, the prevalence of HLA-Cw12, HLA-DR15, HLA-DQ7, and HLA-DPw9 was significantly higher in patients with immunotherapy-induced central hypoadrenalism [41]. In a study conducted on a Japanese population of patients with pituitary disfunction during ICIs, HLA-DR15, B52, and Cw12 were identified as possible predisposing factors [43]. The putative antigens of immunotherapy-induced hypophysitis and hypopituitarism were not completely clarified, despite preliminary studies suggesting ACTH, prolactin, and CTLA-4 as possible disease antigens [44] [45].

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