Autoimmunity Reviews 18 (2019) 102363

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Autoimmune phenomena involving the pituitary gland in children: New developing data about diagnosis and treatment

Alberto Romano[a,1], Donato Rigante[a,b,*,1], Clelia Cipolla[a]

[a] Institute of Pediatrics, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy
[b] Università Cattolica Sacro Cuore, Rome, Italy

ARTICLE INFO

Keywords:
Hypophysitis
Hypopituitarism
Anti-pituitary antibodies
Anti-hypothalamus antibodies
Antidiuretic hormone deficiency
Growth hormone deficiency
Personalized medicine
Innovative biotechnologies
Child

ABSTRACT

The contribution of autoimmune phenomena to dysfunction of hypophysis or hypothalamus is far to be unraveled and also the specific pathways of hypophysitis are poorly understood until now, mostly for the pediatric population. Primary hypophysitis is rare in children and often regarded as an autoimmune disorder, following the evidence of lymphoplasmacytic infiltration in the pituitary gland, detection of anti-pituitary antibodies (APA) and anti-hypotalamus antibodies (AHA) by indirect immunofluorescence on cryostatic sections of human or primate hypophysis and hypothalamus, and coexistence with other autoimmune disorders. The rarity of this condition and the lack of ad hoc studies make hard any assessment of the real incidence of hypophysitis in pediatric patients, and also the role of APA and AHA has been poorly investigated in children with idiopathic hypopituitarism. Potential target autoantigens studied in autoimmune hypophysitis have been various pituitary-specific factors, chaperone proteins, alpha-enolase, secretogranins, chorionic somatomammotropin and intracellular transcription factors. Many clinical features both endocrine and neurologic or systemic can herald the onset of autoimmune hypophysitis. Antidiuretic hormone deficiency with central diabetes insipidus and growth retardation are the most significant presenting symptoms in children with hypophysitis, requiring a careful differential diagnosis with other causes of hypopituitarism, including tumors of the sellar region, differently from adults in whom adrenal insufficiency, hypogonadism, headache or diplopia might be the leading manifestations. Growth hormone deficiency is found in 3/4 of pediatric cases. Five histologic variants of primary hypophysitis have been described: lymphocytic, granulomatous, xanthomatous, IgG4-related and necrotizing: lymphocytic hypophysitis is the most frequent variant in the pediatric sceneries. Children with diagnosis of hypophysitis are also at risk of developing germinomas later in life, and require an extended follow-up in the long-term. Therapeutic options should be differentiated according to the rapidity of disease progression and modality of clinical onset, as acute pictures might require corticosteroids or immunosuppressant agents, while chronic forms may need a conservative management or appropriate hormone replacement therapies. This review updates and summarizes the most recent information related to the autoimmune involvement of hypophysis and hypothalamus in children, discusses the correlations between APA, AHA and disease activity, as well as the recommendations for treatment of primary hypophysitis from the pediatric perspective.

1. General concepts about hypophysitis

Hypophysitis is an acute or chronic inflammation of the pituitary gland and is a rare cause of hypopituitarism, mimicking tumors of the sellar region and causing hormonal deficiencies or variable mass-effect symptoms, which require a meticulous diagnostic work-up [1]. This inflammatory disorder may result in hypophysial and/or hypothalamic dysfunction arising from the destruction of hypophysis or compression of the normal residual gland by edema [2]. In general terms, the anatomic location of pituitary involvement (adenohypophysitis, infundibulo-neurohypophysitis or panhypophysitis) and its apparent cause (primary if "isolated" or secondary if associated with medications, systemic inflammatory disorders, infections and/or other diseases) consent to classify hypophysitis in patients of whatever age [3].

Primary forms of hypophysis dysfunction are characterized by inflammation confined to the pituitary gland, which is often idiopathic, while secondary forms are due to inflammatory processes triggered by a definite etiology or concomitant generalized diseases, which might be

* Corresponding author at: Institute of Pediatrics, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy.
E-mail address: donato.rigante@unicatt.it (D. Rigante).
[1] Both these authors equally contributed to this manuscript.

https://doi.org/10.1016/j.autrev.2019.102363
Received 24 March 2019; Accepted 30 March 2019
Available online 08 August 2019

intracranial or systemic [4]. Five histologic variants of primary hypophysitis have been described: lymphocytic, granulomatous, xanthomatous, IgG4-related and necrotizing [4]. Primary hypophysitis is predominant in adult females (with a female:male ratio of 6:1), but is rare in children. and frequently regarded as an autoimmune disorder: this hypothesis is supported by the evidence of lymphoplasmatic infiltration of the pituitary gland, by the occurrence of anti-pituitary antibodies (APA) and anti-hypotalamus antibodies (AHA), and by the coexistence with other established autoimmune disorders [5–7]. No gender difference can be observed in pediatric patients with primary hypophysitis [7]. Granulomatous, xanthomatous, IgG4-related (or plasmacytic) and necrotizing hypophysitis have been rarely described in children up to now. Lymphocytic forms are the most frequently encountered in pediatric sceneries. The rarity of hypophysitis and lack of ad hoc studies prevent any correct assessment of its true incidence in pediatric patients, and also the pathogenic role of APA and AHA has been poorly investigated in children with idiopathic hypopituitarism [8,9].

In this review we have searched for papers dedicated to hypophysitis in the pediatric age performing a Pubmed-based retrieval of articles using the search terms “hypophysitis”, “adenohypophysitis”, “infundibulo-neurohypophysitis”, “autoimmune hypophysitis”, “anti-pituitary antibodies”, “anti-hypotalamus antibodies”, and “hypopituitarism” matched with “children”, “childhood”, and “pediatric”. After the original search, we used filters to select articles available in English language and articles with available full texts. The final search retrieved 95 articles, of which 11 were exclusively related to pediatric patients: these studies were critically analyzed for the present review.

2. A complex interplay of autoimmune phenomena within the hypothalamic-pituitary axis

Lymphocytic hypophysitis has been reported in patients affected by other autoimmune diseases [10], such as Hashimoto's thyroiditis [11–13], Graves' disease [14,15], Addison's disease [16], diabetes mellitus type 1 [17], atrophic gastritis [11,18], systemic lupus erythematosus [19,20], Sjögren's syndrome [21], primary biliary cirrhosis [22], autoimmune hepatitis [23], and autoimmune polyendocrine syndrome type I/autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (or APECED) [24]. The association of lymphocytic hypophysitis with other autoimmune disorders is usually considered as a frank proof of an autoimmune pathogenesis for hypophysitis, and indeed, according to Rose and Bona criteria [25], the association with other diseases having a clear autoimmune nature is a circumstantial evidence of the autoimmune etiology of the disease. In particular, according to Rose and Bona criteria, direct evidence of an autoimmune pathogenesis is given by the possibility to transfer the disease to recipients by direct transfer of autoantibodies, by the transplacental transmission of pathogenic IgG autoantibodies from an affected mother to the fetus, and by the reproduction of the autoimmune disease in experimental animal models [25]. Further evidence is represented by the association with other autoimmune diseases in the same individual or in the same family, by the presence of lymphocytic infiltration of target-organs, by the statistical association with particular MHC haplotypes or aberrant expression of MHC class II antigens on the affected organs, and by the favourable response to immunosuppressant drugs [25]. On this way, other elements that suggest an autoimmune pathogenesis of primary hypophysitis are improvement of specific symptoms in response to immune suppression, presence of APA or AHA, and lymphoplasmacytic infiltrate in the histological studies [4].

The infiltration of the pituitary gland with lymphocytes is the main pathological feature of lymphocytic hypophysitis: in particular, lymphocytes can infiltrate the whole gland or organize themselves in lymphoid follicles coexisting with plasma cells and, more rarely, whit eosinophils, macrophages and neutrophils. This infiltration disrupts the normal architecture of the gland and its parenchyma, which might be even replaced by fibrotic tissue [26]. Two distinct inflammatory patterns have been identified by Guaraldi et al. [27] and Mirocha et al. [28] for patients diagnosed with lymphocytic hypophysitis. In both, T lymphocytes prevail over B lymphocytes with two different organizations: in the first, Th17+ lymphocytes prevail over T reg ones and infiltrate the gland with a higher number of macrophages, monocytes, granulocytes and NK cells; in the second, lymphocytic infiltration is more organized and made by CD20+ B cells surrounded by CD3+ T cells with abundant T regs, and a pattern similar to lymphoid tissue involved in the immune tolerant phase of chronic infections [28].

Another powerful evidence of an autoimmune etiology for primary hypophysitis is the detection of APA and AHA, which were first reported in 1965 in the sera obtained by patients with postpartum pituitary gland necrosis (also known as Sheehan's syndrome) [10]. Mechanisms that cause the generation of APA and AHA, usually detected by indirect immunofluorecence (IF) on cryostatic sections of human or monkey hypophysis and hypothalamus, could be the same involved in other autoimmune disorders [29]: new antigens are exposed to immune cells, which in turn activate the production of autoantibodies. In this way, a *primum movens* could be an agent that determines a pituitary damage, such as trauma, infection, vascular accident and neoplasm (Fig. 1). However, the diagnostic sensitivity of these markers have been judged low, as they have been detected in many inflammatory conditions and even in healthy subjects [10]. Tanriverdi et al. showed that APA and AHA were present in a group of patients with bacterial and viral meningitis 12 months after the resolution of infection [30]. Guaraldi et al. found that APA and AHA were positive in a significant number of adults and children with past history of head trauma [31]. De Bellis et al. detected APA and AHA in women with Sheehan's syndrome, indicating that they could be the cause of persistent hypopituitarism after the resolution of a previous vascular disorder [32]. All these studies suggested that hypophysial or hypothalamic damage might be the initial trigger contributing to the development of APA and AHA. Anyway, the pituitary/hypothalamus damage alone cannot explain the production of APA and AHA [29]. A recent study of Chiloiro et al. has investigated the association between the production of APA and AHA and presence of specific HLA haplotypes. In particular, they observed a higher incidence of HLA haplotypes typical of celiac disease in patients with autoimmune hypophysitis [33]. The association between APA and celiac disease was also showed by Delvecchio et al., who detected a remarkable prevalence of positive APA-patients with a newly diagnosed celiac disease [34]. In particular, they tested 119 celiac children for APA and compared them with 98 age- and sex-matched controls; APA were detected in 50 patients (42%), but only in 2 controls [34]. This evidence also indicates the relevant role of a genetic predisposition to promote the production of APA and AHA.

The peculiar combination of genetic predisposition, pituitary damage, and immunological setting could be the basis of APA and AHA production, though antigens recognized by APA and AHA are not well known. Ziemnicka et al. found autoantibodies directed against the microsomal fraction of the human pituitary gland in adults originally diagnosed with childhood-onset deficiency of combined pituitary hormones [35], detecting these autoantibodies in 24.2% of patients. Microsomes are small vesicles of different molecular mass originating from membrane fragments of the Golgi apparatus, endoplasmic reticulum and cell membranes, and in their study Ziemnicka et al. indicated many different pituitary microsomal proteins with potential immunogenic properties obtained from human autopsy 24 h after death; however, the most significant were those with a molecular mass of 97, 67, 60, 55 and 36 kDa, respectively. The authors also compared the molecular mass of microsomes with different proteins already described as possible autoantigens in other autoimmune disorders, and showed that the most probably involved ones were the group of chaperones from the endoplasmic reticulum (ER) [35]. ER chaperons are proteins mostly expressed in the endocrine tissues and brain: the way by which they become immunogen is still under study, but a stressing

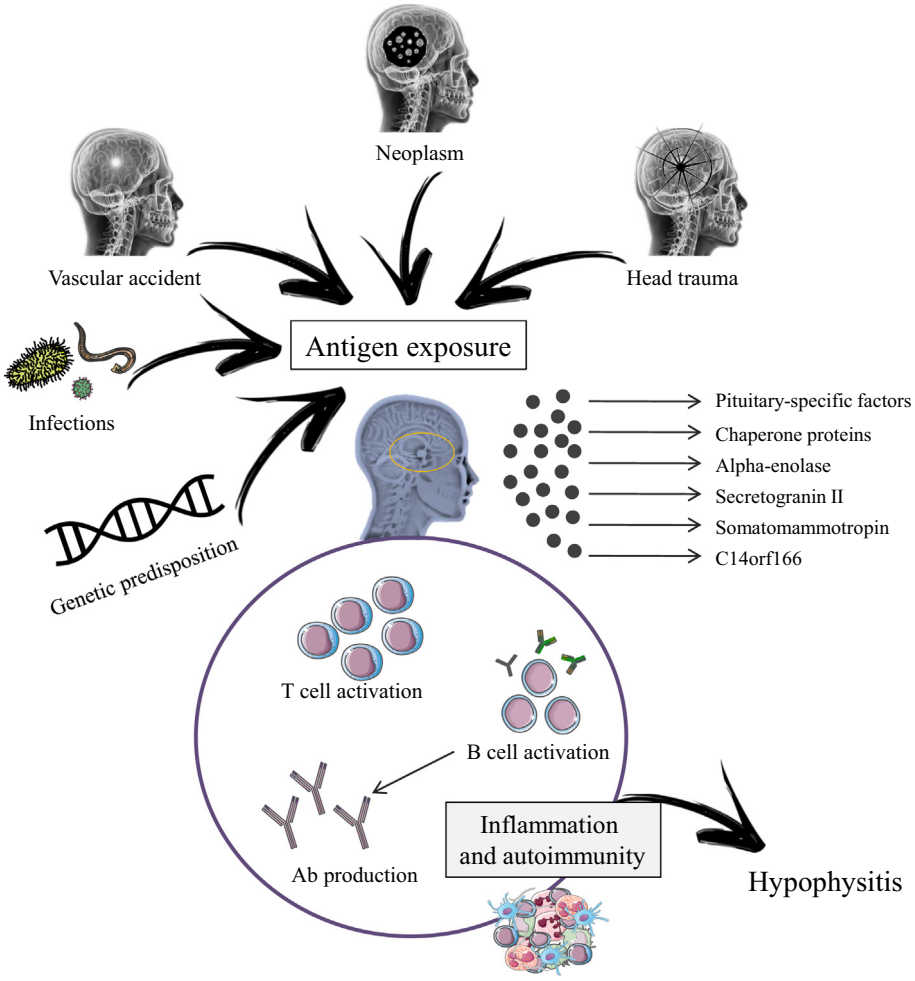

Fig. 1. Summary of the most relevant pathogenetic drivers of autoimmune hypophysitis: infections, vascular accidents, head traumas or cerebral neoplasms could damage the pituitary gland, inducing the exposure of neoantigens such as endoplasmatic reticulum chaperons, pituitary gland specific factors, alpha-enolase, secretogranin II, chorionic somatomammotropin, and chromosome 14 open reading frame 166. In the presence of a genetic predisposition, T and B cells process these neoantigens and activate a targeted immunological response. In particular, B cells produce autoantibodies directed against neoantigens, whereas T cells directly attack and infiltrate the whole gland.

event (for instance, common viral infections during childhood) might increase the expression of ER chaperons and their translocation to the cytosol and cell membranes. These events may potentiate their immunogenic characteristics and promote production and release of autoantibodies.

Further potential antigens investigated in the synthesis of APA and AHA are growth hormone (GH), two novel pituitary-specific proteins, namely pituitary gland specific factor 1a and 2 [36], alpha-enolase [37], secretogranin II [38], chromosome 14 open reading frame 166 (c14orf166, which is an RNA transcription, translation and transport factor), and chorionic somatomammotropin (also known as human placental lactogen) [39]. In particular, the 49 kD alpha-enolase was the first pituitary autoantigen recognized as being potentially involved in the autoimmune process of primary hypophysitis, though this protein is widely expressed in several human tissues and anti-alpha-enolase autoantibodies have a very low diagnostic specificity [37]. The involvement of these proteins and other multiple factors in the generation of APA and AHA requires further investigation (Tables 1 and 2).

APA and AHA have been also isolated in patients with functional pituitary and hypothalamus dysfunction, and even in healthy subjects. Manetti et al. [40] analyzed 1290 patients with thyroid disorders and found APA in 110 of them, with only 36 having a mild or severe GH deficiency; the others did not have any functional pituitary and hypothalamus deficiency [40]. On the same way, also Delvecchio et al. [34] detected APA in children with celiac disease who were not affected by any pituitary and hypothalamus deficiency. These observations show that the presence of APA is not always indicative of hypophysitis, and that these antibodies could be found incidentally.

De Bellis et al. analyzed 36 adult patients with isolated autoimmune organ-specific diseases, positive for high titer-APA, comparing them with 40 patients with isolated autoimmune organ-specific disease, who were negative for APA [41]: they observed that APA-positive patients with a particular IF pattern were prone to develop hypopituitarism. In particular, in patients with organ-specific autoimmune disorders but without pituitary dysfunction, the characterization of pituitary cells targeted by APA at diagnosis may help predicting the features of a subsequent pituitary dysfunction [41]. Instead, APA directed against several types of pituitary hormone-producing cells did not allow to predict both onset and kind of hypopituitarism, which could appear later. Unfortunately, there are no specifically dedicated studies on children.

As reported by Caturegli et al., the timing of measurement of APA has a relevance, because APA may not be produced if the pituitary gland is completely destroyed after an autoimmune attack [26]. For instance, Chiovato et al. found that antibodies against thyroperoxidase, thyroglobulin, and thyrotropin receptor tend to progressively disappear after a complete ablation of the thyroid, indicating that continued antibody production requires autoantigen persistence and that antibodies will decrease over time when the antigenic load also decreases [42]. Indeed, Caturegli et al. hypothesized that the level of APA and AHA should decrease after the disruption of the pituitary gland [26], and when a full-blown hypopituitarism occurs it is possible that APA and AHA disappear. Another important clue that prevents a complete understanding of APA and AHA role in primary hypophysitis is that these antibodies are difficult to detect. Usually APA and AHA can be tested by indirect IF, immunoblotting (IB) and enzyme-linked immunosorbent

Table 1
Main general features of children presenting autoimmune hypophysitis as reported in the medical literature.

First author	Number of patients	Clinical features	MRI findings	Antibodies detected	Histology	Treatment	Complications	Response to treatment	Reference
Gellner	1	Headache, polyuria and polydipsia	8 × 8 mm homogeneous lesion in the posterior pituitary gland and stalk without hyperintensity of the posterior lobe on T1-weighted images	Not tested	Inflammation characterized by lymphocytes, plasma cells, granulocytes and monocytes	High-dose prednisolone (60 mg/m^2/day) administered for 4 weeks, then slowly tapered over a period of 3 months; substitutive therapy with vasopressin	Severe corticosteroid-induced acne, iatrogenic Cushing's syndrome	Resolution of headache, but persisting need of substitutive therapy with vasopressin	#6
Kalra	1	Headache associated with photopsia, nausea, vomiting, diabetes insipidus and adrenal insufficiency	Suprasellar mass extending into the pituitary stalk and hypothalamus, with a cystic center	Anti-pituitary antibodies	Purulent material, which showed necrotic cell debris, chronic inflammatory cells, fragments of normal lamellar bone and dense collagen tissue with chronic inflammation and some benign squamous epithelial cells with focal acute inflammation	Substitutive therapy with vasopressin, cortisol and rhGH	Empty sella	Persisting need of therapy with vasopressin, cortisol and rhGH	#7
Ward	1	GH deficency	Peri-hypophyseal "halo effect" after gadolinium enhancement	Anti-pituitary antibodies reactive to a 43–45 kDa protein	Not reported	rhGH therapy, immune-suppressive therapy with cyclosporin A	Not reported	Not reported	#24
Delvecchio	50	No symptoms	Not performed	Anti-pituitary antibodies	Not performed	Undone	Not reported	No treatment	#34
Ziemnicka	62 (adults with childood onset)	Seventeen of these patients had been previously treated with rhGH	Hypoplasia of the anterior lobe (40 patients), hypoplasia of the anterior lobe plus pituitary stalk (14 patients), interruption plus ectopy of the posterior pituitary lobe (3 patients), hypoplasia of the anterior lobe plus cystic lesions (3 patients), hyperintense signal from the pituitary gland (2 patients)	Anti-microsomal antibodies in 24.2% of patients	Not reported	Not reported	Not reported	Not reported	#35
Bensing	6	GH deficency	Not reported	3/6 positive for antibodies against guinea pig anterior pituitary cells	Not reported	Not reported	Not reported	Not reported	#38
Bettendorf	1	Diabetes insipidus	Thickened pituitary stalk	Not reported	Active hypophysitis with lymphocytic infiltrates and necrosis	High-dose dexamethasone, stereotactic radiation therapy	Panhypopituitarism, germinoma	Temporary response to dexamethasone	#50
Mikami-Terao	1	Polyuria, polydipsia, fatigue, headache, and pubertal arrest	Enlarged pituitary gland and mass-lesion in the pituitary stalk and inferior hypothalamus, that was isointense on T1-weighted images and enhanced after gadolinium	Not reported	Mononuclear inflammatory infiltrates with germinal center formation	Substitutive therapy with vasopressin, oral prednisolone (1 mg/kg/day) for 4 weeks	Visual loss in the left eye, germinoma developed 1 year after diagnosis, persistent diabetes insipidus	Temporary response to prednisolone	#53
Gutenberg	1		Intra- and supra-sellar mass, measuring 22 × 16 × 17 mm			Substitutive therapy with vasopressin, intravenous	Germinoma developed 6 weeks after diagnosis	Temporary response to corticosteroids	#54

(*continued on next page*)

Table 1 (*continued*)

First author	Number of patients	Clinical features	MRI findings	Antibodies detected	Histology	Treatment	Complications	Response to treatment	Reference
		Blurred vision, fatigue, polyuria and polydipsia		No pituitary antibodies were found	Anterior pituitary lobe heavily infiltrated by mononuclear cells	methylprednisolone(30 mg/kg/day for 3 days, followed by oral prednisone for 2 weeks)			

Table 2
Main general symptoms of autoimmune hypophysitis occurring in children and adults (revised from Gellner et al. [6]).

Clinical findings	Children (%)	Adults (%)
Headache	17%	50–70%
Diabetes insipidus	85%	14–20%
Growth hormone deficiency	76%	36–54%
Hypothyroidism	29%	49–60%
Adrenal insufficiency	20%	57–65%
Panhypopituitarism	11%	66–97%
Hyperprolactinemia	8%	20–38%
Visual disturbance	32%	40–43%
Vomiting	8%	25%
Gonadal dysfunction	32%	40–52%
Development of germinoma	3%	25–50%

assay [43–45]. Caturegli et al. compared IF and IB, finding that IB is more sensitive and specific than IF in predicting the histologically-proven hypophysitis [26]. Lymphocytic hypophysitis is therefore a frank autoimmune pathology, but still not enough is clearly known about pathogenesis, and the clinical applicability of APA and AHA in the routine diagnosis remains limited by their low diagnostic sensitivity and specificity.

3. A tangled clinical scenario with protean faces

The number of children with autoimmune hypophysitis described in the medical literature is small, with < 100 cases reported, of which only a few are biopsy-proven [6,7]. The autoimmune process targets different pituitary cells followed by nonselective gland destruction, and at autopsy the pituitary gland may reveal a significant atrophy. General signs and symptoms of hypophysitis at the time of diagnosis depend on the degree of pituitary involvement and rapidity of disease progression with subsequent pituitary hormone abnormalities [4,27,46,47]. Primary hypophysitis involves more frequently the anterior pituitary gland, and patients might typically display hormonal deficiencies and protean symptoms related to mass-effect from either pituitary enlargement or edema with pituitary/hypothalamic dysfunction. Pediatric sceneries of hypophysitis are characterized by clinical presentations quite different than in adults. Kalra et al. showed that the most common presenting symptoms in children are caused by antidiuretic hormone (ADH) deficiency (85%), compared with 14-to-20% of adults [7]. GH deficiency was found in 76% of pediatric cases, compared with 36-to-54% of adults, while follicle stimulating hormone (FSH)/luteinizing hormone (LH), thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) deficiencies were less common than in adults (32%, 29% and 20%, respectively, compared with 40-to-52%, 49-to-60%, 57-to-65% of adults) [7]. In particular, contrarily to other causes of hypopituitarism, an impaired secretion of ACTH and TSH is very frequent in the early phase of primary hypophysitis, putting these patients at increased risk of life-threatening adrenal insufficiency [7]. If the patient presents signs and symptoms referred to hypocortisolism and hypothyroidism the administration of thyroxin should follow corticosteroid therapy to restore adrenocortical function and prevent acute adrenal insufficiency. Increased levels of prolactin (PRL) can be also observed in both hypophysitis and pituitary adenomas, in association with abnormal levels of FSH and LH. Hypogonadism can also occur through a direct damage of gonadotropic cells due to hypophysitis-related inflammation. In particular, hyperprolactinemia can be found in 8% of children with hypophysitis, compared with 20-to-38% of adults [7]. Headache and visual disturbances have been less frequently reported in children (17% and 8% of cases, respectively, compared with 50-to-70% and 40-to-43% of adults) [7].

As central diabetes insipidus and growth retardation are crucial symptoms in children with primary hypophysitis, a complete differential diagnosis should also consider other disorders displaying these

hormonal deficiencies, such as the more frequent intracranial germinoma, Langerhans cell histiocytosis (LCH) and craniopharyngioma [48]. Moreover, children with a presumptive diagnosis of hypophysitis are at risk of developing germinomas later in life (up to 3 years after the initial diagnosis), requiring a comprehensive extended follow-up in the long-term [7,49]. Germinomas are rare brain tumors primarily affecting prepubertal children, and they are an established cause of secondary hypophysitis [50–53]. Moreover, germinomas arising in the sellar and parasellar regions are difficult to differentiate from childhood hypophysitis because of similar clinical features (diabetes insipidus, GH deficiency, visual disturbances). This differentiation, nevertheless, is critical due to the different treatments needed.

Biopsy-proven cases of primary hypophysitis are few in children and adolescents, and an intracranial germ cell tumor should be considered the most likely diagnosis in children below 10 years [6]. Tumor markers such as α-fetoprotein, β-human chorionic gonadotropin and placental alkaline phosphatase in the cerebrospinal fluid may be useful for diagnosis of germinoma. Pituitary biopsy is the gold-standard for differentiating the two conditions, although germinomas can have a marked lymphocytic infiltrate making problematic the differential diagnosis with local inflammation [54]. Finally, it is known that hypopituitarism caused by sellar germinoma can precede for years a visible pituitary mass, and prolonged symptomatic periods may also be common prior to diagnosis [54].

In adult patients, when the inflammation involves the anterior pituitary gland, headache is the most common presenting symptom, occurring in about half of patients. Visual symptoms due to compression of the optic nerves and/or cranial nerves III, IV and VII can occur in a minority of cases [4,26,55]. Cavernous carotid artery occlusion is a rare complication of hypophysitis [56–59]. Onset of headache can be insidious, subacute and even mimic apoplexy [55,60,61]. Less frequently, inflammation can involve the posterior pituitary gland and the stalk: these young adults with infundibulo-neurohypophysitis present diabetes insipidus and less commonly other hormone deficiencies. As expected, signs of both anterior and posterior pituitary involvement coexist in panhypophysitis. A recent case series of adult patients has highlighted that the secretion of gonadotropins can be impaired [55]. Additionally, GH deficiency and hyperprolactinemia might also occur [55].

Granulomatous hypophysitis can be associated with more severe symptoms than in lymphocytic hypophysitis, which may be oppressive headache combined with variable signs of hypopituitarism and chiasmal compression [55,62–64]. The most common symptoms of idiopathic granulomatous hypophysitis at presentation in 84 adult patients were headache (61%), visual changes (40%), polyuria/polydipsia (27%), and cranial nerve palsies (27%); panhypopituitarism and diabetes insipidus were found in 49% and 27% of these adult cases, respectively [65]. Clinical data regarding xanthomatous and IgG4-related hypophysitis are less robust, due to the extreme rarity of these variants. However, Gutenberg et al. found that xanthomatous hypophysitis did not cause any chiasmal compression and was associated with a lower risk of diabetes insipidus and less severe anterior pituitary impairment than other forms of hypophysitis. In particular, FSH, LH and GH deficiencies were more common than TSH and ACTH deficiencies [64]. IgG4-related hypophysitis, instead, is more frequently in middle-aged and elderly males and characterized by lymphoplasmacytic infiltration with predominant IgG4-positive plasma cells in the affected tissues and high level of serum IgG4 [66]. This condition might involve one or multiple organs, including lymph nodes, pancreas, liver, salivary and lacrimal glands, retroperitoneum, aorta, pericardium, thyroid, lungs, kidney, skin, stomach, prostate and ovaries [66]. This form of hypophysitis frequently involves both the pituitary gland and stalk (about 65% of cases), causing panhypopituitarism, anterior hypopituitarism and central diabetes insipidus in 50%, 25% and 18% of cases, respectively [67]. Intrachiasmal abscesses spreading to the cavernous sinus have also been reported in women with IgG4-related hypophysitis [68,69].

4. Diagnostic algorithm for children with primary hypophysitis

Differential diagnosis of hypophysitis requires histopathologic evaluation for a definite exclusion of pituitary adenoma, hypophysial metastases, sellar and parasellar tumors like craniopharyngioma or Rathke's cleft cyst (a non-neoplastic epithelium-lined cyst arising from the embryologic remnants of Rathke's pouch in the pituitary gland), germinoma, glioma, meningioma, pituicytoma (a rare low-grade glial neoplasm that originates from the neurohypophysis), chordoma (a rare neoplasm arising from cellular remnants of the notochord), teratoma, dermoid and epidermoid, but also abscesses or a physiological hypertrophy of the pituitary gland in children and adolescents (especially pubertal females) [70]. Also pituitary hyperplasia associated with pregnancy should be excluded in young women [70].

A first approach to patients with suspected symptoms of primary hypophysitis should include the evaluation of pituitary gland-related hormonal profile, such as cortisol, ACTH, insulin-growth factor-1, GH, estradiol/testosterone, LH, FSH, free thyroxine, TSH, prolactin, plasma/urine osmolality and electrolytes. The level of antidiuretic hormone should be measured with urinary osmolarity, that usually is higher than plasmatic osmolarity in diabetes insipidus [55]. Secondary hypophysitis due to systemic diseases can be assessed by checking routine baseline investigations, such as full blood cell count, renal, liver and bone markers, C-reactive protein, erythrocyte sedimentation rate, serology for syphilis, tuberculosis-specific tests and coltural studies for bacterial or fungal infections, eventually associated with peripheral blood smear, bone marrow aspirate, immunoglobulins and flow cytometry immunophenotyping (if immunologic abnormalities are suspected) [55].

After this first-line diagnostic work-up, brain magnetic resonance imaging (MRI) is crucial for diagnosis: it typically demonstrates an increased size of hypophysis with uniform enhancement after contrast and potential extension to the hypothalamus. Involvement of the cavernous sinus may be responsible of headache, diplopia and cranial nerve palsies. A recent study has shown that only 4% of stalk lesions are caused by primary hypophysitis. More than one half of stalk abnormalities on MRI are represented by neoplastic processes, and half of these are metastases [71]. Moreover, many diseases that can mimic primary hypophysitis might respond to the same treatment required by hypophysitis, i.e. glucocorticoids. Indeed, glucocorticoids are part of the standard treatment regimens for LCH and Erdheim-Chester disease (ECD), which is a rare non-Langerhans form of histiocytosis [72,73], whereas temporary responses to steroids have been observed in lymphoma and intracranial germinoma [74–76]. A positive response in germinoma is likely due to the steroidal effects on tumor-infiltrating lymphocytes [54,77,78]. As a consequence, brain MRI should be performed before starting any treatment in patients with suspected hypophysitis.

In the pre-gadolinium era the characteristics of hypophysitis on MRI included homogeneous pituitary enlargement with symmetrical suprasellar expansion, chiasm displacement, stalk swelling (an enlarged pituitary stalk can also be found in other intracranial pathologies, like sarcoidosis, metastases, LCH, germinoma, craniopharyngioma, astrocytoma, pituitary adenoma and ECD), loss of bright spot of neurohypophysis in the case of posterior pituitary involvement (the bright spot might be absent in up to 20% of healthy subjects) during acute and subacute phases. Pituitary atrophy and empty sella could appear during the chronic phase of hypophysitis [79].

A striking feature of primary hypophysitis on MRI in the post-gadolinium era is the homogeneous enhancement of the pituitary mass with “dural tail sign” (thickening of the enhanced dura that resembles a tail extending from a mass). However, the dural tail sign is not specific of hypophysitis, being also observed in meningioma (most frequently) and other different intracranial pathologies, like lymphoma, multiple myeloma, glioblastoma multiforme, chordoma, schwannoma,

pleomorphic xanthoastrocytoma, hemangiopericytoma, granulomatosis with polyangitis, sarcoidosis, medulloblastoma, eosinophilic granuloma, ECD, pituitary adenoma and apoplexy [80]. On the contrary, unilateral endosellar masses or nonhomogeneously-expanding pituitary masses with asymmetrical extension might suggest a pituitary adenoma. Cystic and necrotic areas may be frequently observed in macroadenomas (> 1 cm) via MRI, while the dural tail is usually absent [80]. Hence, the combination of clinical manifestations, laboratory tests and brain MRI assessment can suggest a primary hypophysitis, though histologic evaluation remains crucial [55]. Obtaining histology requires a neurosurgical biopsy or resection of sellar or suprasellar tissue, and this procedure might cause morbidity by itself: this decision should be advised through a multidisciplinary approach and reserved to the most severe cases, displaying visual acuity impairment due to gland compression or infiltration, who are obviously nonresponsive to medical therapies [55].

APA and AHA are not routinely evaluated to date. As previously said, APA and AHA are difficultly measured and have low sensitivity and specificity for primary hypophysitis [9]. Further specific autoantibodies (such as anti-nuclear, anti-dsDNA, anti-parietal cell antibodies, etc.) are useful in the assessment of hypophysitis associated with Hashimoto's thyroiditis [11–13], Graves' disease [14,15], Addison's disease [16], diabetes mellitus type 1 [17], atrophic gastritis [11,18], systemic lupus erythematosus [19,20], Sjögren's syndrome [21], primary biliary cirrhosis [22], autoimmune hepatitis [23], and APECED [24]. In conclusion, a relevant and considerable challenge in the management of young patients with autoimmune hypophysitis is to establish diagnosis by minimally invasive methods through a step-by-step process that requires the exclusion of all causes of hypophysitis and the combination of clinical, radiological and laboratory investigations, even if histologic assessment is the gold-standard for a definite diagnosis.

5. Treatment strategies of autoimmune hypophysitis: controversies and truths

The different expression of primary hypophysitis in children may require different therapeutic strategies, also considering that this autoimmune disease may be self-limited and that spontaneous remissions have been reported. Indeed, the natural history of hypophysitis may be unpredictable, from spontaneous recovery with complete remission of clinical, laboratory and imaging features to severe pictures with permanent hormonal and neurological impairment. Most treatment strategies are symptomatic, aiming at reducing the size of the pituitary gland. Of course, the type of treatment is dictated by rapidity of onset and severity of clinical signs. A conservative management is recommended for most cases of lymphocytic hypophysitis, unless symptoms become progressively severe [81].

Optic nerve compression and other cranial nerve palsies or severe headache are general indications for starting treatment [3]. Therapeutic options are different in the acute and chronic phases [82]: glucocorticoid deficiency should be first treated to prevent an acute potential adrenal insufficiency, and glucocorticoid replacement is mandatory in the early phase of hypophysitis. Because adrenal insufficiency could partially mask the presence of central diabetes insipidus, monitoring patients for the development of diabetes insipidus is important after replacing glucocorticoids.

Surgical options by trans-sphenoidal surgery may be necessary in the acute phase of hypophysitis if symptoms and/or signs deriving from a mass-effect are present [83–85]. Corticosteroids tend to improve the swelling of both pituitary gland and stalk: at high doses they are reported as a first-line or second-line therapy after neurosurgery in reducing pituitary size (with successful results in 75% of cases) and improving endocrine dysfunctions [10]. The most commonly used corticosteroids are prednisone, hydrocortisone and methylprednisolone. Some anterior pituitary deficits can be resolved by corticosteroids, even at low-doses [86]. Immunosuppressant drugs such as azathioprine, methotrexate and cyclosporine have been successfully used in glucocorticoid-resistant cases, but their long-term efficacy still needs to be confirmed [87].

Treatment of the chronic phase is aimed at restoring adequate hormone levels with appropriate replacement therapy, recovering secondary adrenal insufficiency, hypogonadism, hypothyroidism and GH deficiency, if present, due to the autoimmune disease “per se” or as result of neurosurgery. Hormone replacement should be done according to the current Endocrine Society Clinical Practice Guidelines [88]. Dopamine agonists (bromocriptine, cabergoline) can lower hyperprolactinemia and improve visual field abnormalities [89]. Indeed, it is known that high levels of prolactin can contribute to the perpetuation of many immune processes through the proinflammatory effects of this hormone [90,91], as shown in prolactinoma-related hyperprolactinemia [92].

Pituitary surgery (gross total resection or partial resection) provides a definitive histological diagnosis of hypophysitis and might promptly relieve compressive symptoms, which if present are a strong indication for the surgical approach. Surgery should be performed in cases with severe and progressive visual acuity impairment or abnormal ocular movements due to gland compression or infiltration, which are nonresponsive to medical treatment [93]. Corticosteroids, although effective, can cause numerous side effects. Therefore, novel immunotherapies with more specific mechanisms of action are being proved, such as infliximab and rituximab. Treatment with stereotactic radiosurgery and fractionated radiotherapy has also been reported in a few patients, especially when the disease is corticosteroid-dependant or refractory [94,95].

6. Conclusive remarks

In conclusion, autoimmune hypophysitis is an inflammatory process of the pituitary gland which is uncommon in children. It is divided into three types based on the specific pituitary area involved: adenohypophysitis, in which only anterior pituitary gland is involved, infundibuloneurohypophysitis, when the inflammation involves the posterior lobe, and panhypophysitis when the disease globally involves both anterior and posterior lobe and the infundibulum. In addition, hypophysitis can be classified according to the etiology in secondary or primary, following the concomitant presence of other triggering disorders or not. Finally, five histologic variants of primary hypophysitis have been described: lymphocytic, granulomatous, xanthomatous, IgG4-related (or plasmacytic) and necrotizing, but mostly the first has been encountered in pediatric patients. The most common presenting symptom in children is central diabetes insipidus, caused by antidiuretic hormone deficiency, but GH deficiency is also frequent, combined with variable mass-effect signs deriving from either pituitary enlargement or focal edema. Biopsy is considered the most relevant diagnostic tool in primary hypophysitis to exclude tumors of the sellar region, but it should be cautiously discussed with different medical advisors. The different expressions of this autoimmune disease require many optional therapeutic strategies, also because spontaneous remissions can occur. Options are different in the acute and chronic phase of hypophysitis, as the first might require only corticosteroids or immunosuppressant agents, while replacement therapies in the later phases should be aimed at optimizing hormone levels.

Future studies are needed to identify biologic clues that characterize the subset of children with autoimmune hypophysitis having the worst outcome as well as to optimize treatment strategies based on the effective risk of progressive sequelae.

References

[1] Carmichael JD. Update on the diagnosis and management of hypophysitis. Curr Opin Endocrinol Diabetes Obes 2012;19:314–21.

[2] Bellastella G, Maiorino MI, Bizzarro A, Giugliano D, Esposito K, Bellastella A, et al. Revisitation of autoimmune hypophysitis: knowledge and uncertainties on pathophysiological and clinical aspects. Pituitary 2016;19:625–42.
[3] Faje A. Hypophysitis: evaluation and management. Clin Diabetes Endocrinol 2016;2:15.
[4] Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune hypophysitis. Endocr Rev 2005;26:599–614.
[5] Murray PG, Clayton PE. De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, ... Vinik A, editors. Disorders of growth hormone in childhood. South Dartmouth (MA): MDText.com, Inc; 2000.
[6] Gellner V, Kurschel S, Scarpatetti M, Mokry M. Lymphocytic hypophysitis in the pediatric population. Childs Nerv Syst 2008;24:785–92.
[7] Kalra AA, Riel-Romero RM, Gonzalez-Toledo E. Lymphocytic hypophysitis in children: a novel presentation and literature review. J Child Neurol 2011;26:87–94.
[8] Cocco C, Brancia C, Corda G, Ferri GL, et al. Int J Mol Sci 2017:18(11).
[9] De Bellis A, Pane E, Bellastella G, Sinisi AA, Colella C, Giordano R, et al. Detection of anti-pituitary and anti-hypothalamus antibodies to investigate the role of pituitary or hypothalamic autoimmunity in patients with selective idiopathic hypopituitarism. Clin Endocrinol 2011;75:361–6.
[10] Falorni A, Minarelli V, Bartoloni E, Alunno A, Gerli R. Diagnosis and classification of autoimmune hypophysitis. Autoimmun Rev 2014;13:412–6.
[11] Goudie RB, Pinkerton PH. Anterior hypophysitis and Hashimoto's disease in a woman. J Pathol Bacteriol 1962;83:584–5.
[12] Cosman F, Post KD, Holub DA, Wardlaw SL. Lymphocytic hypophysitis. Report of 3 new cases and review of the literature. Medicine (Baltimore) 1989;68:240–56.
[13] Patel MC, Guneratne N, Haq N, West TE, Weetman AP, Clayton RN. Peripartum hypopituitarism and lymphocytic hypophysitis. QJM 1995;88:571–80.
[14] Crock PA. Cytosolic autoantigens in lymphocytic hypophysitis. J Clin Endocrinol Metab 1998;83:609–18.
[15] Bayram F, Kelestimur F, Ozturk F, Selcuklu A, Patiroglu TE, Beyhan Z. Lymphocytic hypophysitis in a patient with Graves' disease. J Endocrinol Investig 1982;21:193–7.
[16] Sobrinho-Simoes M, Brandao A, Paiva ME, Vilela B, Fernandes E, Carneiro-Chaves F. Lymphoid hypophysitis in a patient with lymphoid thyroiditis, lymphoid adrenalitis, and idiopathic retroperitonealfibrosis. Arch Pathol Lab Med 1985;109:230–3.
[17] Hashimoto K, Takao T, Makino S. Lymphocytic adenohypophysitis and lymphocytic adenoinfundibuloneurohypophysitis. Endocr J 1997;44:1–10.
[18] Mazzone T, Kelly W, Ensinck J. Lymphocytic hypophysitis. Associated with antiparietal cell antibodies and vitamin B12 deficiency. Arch Intern Med 1983;143:1794–5.
[19] Hashimoto K, Asaba K, Tamura K, Takao T, Nakamura T. A case of lymphocytic infundibuloneurohypophysitis associated with systemic lupus erythematosus. J Endocrinol Investig 2002;49:605–10.
[20] Hasegawa Y, Matsumoto M, Kamimura A, Yamamoto M. A case of systematic lupus erythematosus with autoimmune hypophysitis. Nippon Naika Gakkai Zasshi 1993;82:582–3.
[21] Li JY, Lai PH, Lam HC, Lu LY, Cheng HH, Lee JK, et al. Hypertrophic cranial pachymeningitis and lymphocytic hypophysitis in Sjogren's syndrome. Neurology 1999;52:420–3.
[22] Nishiki M, Murakami Y, Kashimura K, Sohmiya M, Tanaka J, Yabe J, et al. A case of autoimmune hypophysitis associated with asymptomatic primary biliary cirrhosis. Endocr J 1998;45:697–700.
[23] Pinol V, Cubiella J, Navasa M, Fernández J, Halperin I, Bruguera M, et al. Autoimmune hepatitis associated with thyroiditis and hypophysitis. A case report. Gastroenterol Hepatol 2000;23:123–5.
[24] Ward L, Paquette J, Seidman E, Huot C, Alvarez F, Crock P, et al. Severe autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy in an adolescent girl with a novel AIRE mutation: responsive to immunosuppressive therapy. J Clin Endocrinol Metab 1999;84:844–52.
[25] Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). Immunol Today 1993;14:426–30.
[26] Caturegli P, Lupi I, Landek-Salgado M, Kimura H, Rose NR. Pituitary autoimmunity: 30 years later. Autoimmun Rev 2008;7:631–7.
[27] Guaraldi F, Giordano R, Grottoli S, Ghizzoni L, Arvat E, Ghigo E. Pituitary Autoimmunity. Front Horm Res 2017;48:48–68.
[28] Mirocha S, Elagin RB, Salamat S, Jaume JC. T regulatory cells distinguish two types of primary hypophysitis. Clin Exp Immunol 2009;155:403–11.
[29] Elkon K, Casali P. Nature and functions of autoantibodies. Nat Clin Pract Rheumatol 2008;4:491–8.
[30] Tanriverdi F, De Bellis A, Teksahin H, Alp E, Bizzarro A, Sinisi AA, et al. Prospective investigation of pituitary functions in patients with acute infectious meningitis: is acute meningitis induced pituitary dysfunction associated with autoimmunity? Pituitary 2012;15:579–88.
[31] Guaraldi F, Grottoli S, Arvat E, Ghigo E. Hypothalamic-pituitary autoimmunity and traumatic brain injury. J Clin Med 2015;4:1025–35.
[32] De Bellis A, Kelestimur F, Sinisi AA, Ruocco G, Tirelli G, Battaglia M, et al. Anti-hypothalamus and anti-pituitary antibodies mat contribute to perpetuate the hypopituitarism in patients with Sheehan's syndrome. Eur J Endocrinol 2008;158:147–52.
[33] Chiloiro S, Capoluongo ED, Tartaglione T, Bianchi A, Giampietro A, Angelini F, et al. Human leucocyte antigens coeliac haplotypes and primary autoimmune hypophysitis in Caucasian patients. Clin Endocrinol 2018;88:692–9.
[34] Delvecchio M, De Bellis A, Francavilla R, Rutigliano V, Predieri B, Indrio F, et al. Anti-pituitary antibodies in children with newly diagnosed celiac disease: a novel finding contributing to linear-growth impairment. Am J Gastroenterol 2010;105:691–6.
[35] Ziemnicka K, Gut P, Goła M, Dworacki G, Wrotkowska E, Stajgis M, et al. Pituitary microsomal autoantibodies in patients with childhood onset combined pituitary hormone deficiency: an antigen identification attempt. Arch Immunol Ther Exp 2016;64:485–95.
[36] Tanaka S, Tatsumi KI, Kimura M, Takano T, Murakami Y, Takao T, et al. Detection of autoantibodies against the pituitary-specific proteins in patients with lymphocytic hypophysitis. Eur J Endocrinol 2002;147:767–75.
[37] O'Dwyer DT, Smith AI, Matthew ML, Andronicos NM, Ranson M, Robinson PJ, et al. Identification of the 49-kDa autoantigen associated with lymphocytic hypophysitis as [alpha]-enolase. J Clin Endocrinol Metab 2002;87:752–7.
[38] Bensing S, Fetissov SO, Mulder J, Perheentupa J, Gustafsson J, Husebye ES, et al. Pituitary autoantibodies in autoimmune polyendocrine syndrome type 1. Proc Natl Acad Sci U S A 2007;104:949–54.
[39] Lupi I, Broman KW, Tzou SC, Gutenberg A, Martino E, Caturegli P. Novel autoantigens in autoimmune hypophysitis. Clin Endocrinol 2008;69:269–78.
[40] Manetti L, Lupi I, Morselli LL, Albertini S, Cosottini M, Grasso L, et al. Prevalence and functional significance of anti-pituitary antibodies in patients with autoimmune and non-autoimmune thyroid diseases. J Clin Endocrinol Metab 2007;92:2176–81.
[41] De Bellis A, Dello Iacovo A, Bellastella G, Savoia A, Cozzolino D, Sinisi AA, et al. Characterization of pituitary cells targeted by anti-pituitary antibodies in patients with isolated autoimmune diseases without pituitary insufficiency may help to foresee the kind of future hypopituitarism. Pituitary 2014;17:457–63.
[42] Chiovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M, Masserini L, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med 2003;139:346–51.
[43] Bottazzo GF, Pouplard A, Florin-Christensen A, Doniach D. Autoantibodies to prolactin-secreting cells of human pituitary. Lancet 1975;2:97–101.
[44] Crock PA, Salvi M, Miller A, Wall J, Guyda H. Detection of anti-pituitary antibodies by immunoblotting. J Immunol Methods 1993;162:31–40.
[45] Takanashi K, Inukai T, Ogino K, Takenura Y. A case of lymphocytic infundibuloneurohypophysitis showing diabetes insipidus with Hashimoto's thyroiditis. Sogo Rinsho 1998;47:1050–5.
[46] Buxton N, Robertson I. Lymphocytic and granulocytic hypophysitis: a single centre experience. Br J Neurosurg 2001;15:242–5.
[47] Caturegli P, Di Dalmazi G, Lombardi M, Grosso F, Larman HB, Larman T, et al. Hypophysitis secondary to cytotoxic t-lymphocyte-associated protein 4 blockade: insights into pathogenesis from an autopsy series. Am J Pathol 2016;186:3225–35.
[48] Gan HW, Bulwer C, Spoudeas H. De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, ... Vinik A, editors. Pituitary and hypothalamic tumor syndromes in childhood. South Dartmouth (MA): MDText.com, Inc; 2000.
[49] Di Iorgi N, Morana G, Maghnie M. Pituitary stalk thickening on MRI: when is the best time to re-scan and how long should we continue re-scanning for? Clin Endocrinol 2015;83:449–55.
[50] Bettendorf M, Fehn M, Grulich-Henn J, Selle B, Darge K, Ludecke DK, et al. Lymphocytic hypophysitis with central diabetes insipidus and consequent panhypopituitarism preceding a multifocal, intracranial germinoma in a prepubertal girl. Eur J Pediatr 1999;158:288–92.
[51] Nishiuchi T, Imachi H, Murao K, Fujiwara M, Sato M, Nishiuchi Y, et al. Suprasella germinoma masquerading as lymphocytic hypophysitis associated with central diabetes insipidus, delayed sexual development, and subsequent hypopituitarism. Am J Med Sci 2010;339:195–9.
[52] Ozbey N, Sencer A, Tanyolac S, Kurt R, Sencer S, Bilgic B, et al. An intrasella germinoma with normal cerebrospinal fluid beta-HCG concentrations misdiagnosed as hypophysitis. Hormones (Athens) 2006;5:67–71.
[53] Mikami-Terao Y, Akiyama M, Yanagisawa T, Takahashi-Fujigasaki J, Yokoi K, Fukuoka K, et al. Lymphocytic hypophysitis with central diabetes insipidus and subsequent hypopituitarism masking a suprasella germinoma in a 13-year-old girl. Childs Nerv Syst 2006;22:1338–43.
[54] Gutenberg A, Bell JJ, Lupi I, Tzou SC, Landek-Salgado MA, Kimura H, et al. Pituitary and systemic autoimmunity in a case of intrasellar germinoma. Pituitary 2011;14:388–94.
[55] Honegger J, Schlaffer S, Menzel C, Droste M, Werner S, Elbelt U, et al. Diagnosis of primary hypophysitis in Germany. J Clin Endocrinol Metab 2015;100:3841–9.
[56] Leung GK, Lopes MB, Thorner MO, Vance ML, Laws Jr. ER. Primary hypophysitis: a single-center experience in 16 cases. J Neurosurg 2004;101:262–71.
[57] Peruzzotti-Jametti L, Strambo D, Sangalli F, De Bellis A, Comi G, Sessa M. Bilateral intracavernous carotid artery occlusion caused by invasive lymphocytic hypophysitis. J Stroke Cerebrovasc Dis 2012;21:918.
[58] Ikeda J, Kuratsu J, Miura M, Kai Y, Ushio Y. Lymphocytic adenohypophysitis accompanying occlusion of bilateral internal carotid arteries-case report. Neurol Med Chir (Tokyo) 1990;30:346–9.
[59] Melgar MA, Mariwalla N, Gloss DS, Walsh JW. Recurrent lymphocytic hypophysitis and bilateral intracavernous carotid artery occlusion. An observation and review of the literature. Neurol Res 2006;28:177–83.
[60] Minakshi B, Alok S, Hillol KP. Lymphocytic hypophysitis presenting as pituitary apoplexy in a male. Neurol India 2005;53:363–4.
[61] Husain Q, Zouzias A, Kanumuri VV, Eloy JA, Liu JK. Idiopathic granulomatous hypophysitis presenting as pituitary apoplexy. J Clin Neurosci 2014;21:510–2.
[62] Jain A, Dhanwal DK. A rare case of autoimmune hypophysitis presenting as temperature dysregulation. J Clin Diagn Res 2015;9:9–10.
[63] Chiloiro S, Tartaglione T, Angelini F, Bianchi A, Arena V, Giampietro A, et al. An overview of diagnosis of primary autoimmune hypophysitis in a prospective single-center experience. Neuroendocrinology 2017;104:280–90.
[64] Gutenberg A, Hans V, Puchner MJ, Kreutzer J, Bruck W, Caturegli P, et al. Primary hypophysitis: clinical-pathological correlations. Eur J Endocrinol 2006;155:101–7.

[65] Hunn BH, Martin WG, Simpson Jr. S, McLean CA. Idiopathic granulomatous hypophysitis: a systematic review of 82 cases in the literature. Pituitary 2014;17:357–65.
[66] Decker L, Crawford AM, Lorenzo G, Stippler M, Konstantinov KN, SantaCruz K. IgG4-related hypophysitis: case report and literature review. Cureus 2016;8:e907.
[67] Shikuma J, Kan K, Ito R, Hara K, Sakai H, Miwa T, et al. Critical review of IgG4-related hypophysitis. Pituitary 2017;20:282–91.
[68] Kanoke A, Ogawa Y, Watanabe M, Kumabe T, Tominaga T. Autoimmune hypophysitis presenting with intracranial multi-organ involvement: three case reports and review of the literature. BMC Res Notes 2013;6:560.
[69] Hadjigeorgiou GF, Lund EL, Poulsgaard L, Feldt-Rasmussen U, Rasmussen AK, Wegener M, et al. Intrachiasmatic abscess caused by IgG4-related hypophysitis. Acta Neurochir 2017;159:2229–33.
[70] Allix I, Rohmer V. Hypophysitis in 2014. Ann Endocrinol (Paris) 2015;76:585–94.
[71] Turcu AF, Erickson BJ, Lin E, Guadalix S, Schwartz K, Scheithauer BW, et al. Pituitary stalk lesions: the Mayo Clinic experience. J Clin Endocrinol Metab 2013;98:1812–8.
[72] Cives M, Simone V, Rizzo FM, Dicuonzo F, Cristallo Lacalamita M, Ingravallo G, et al. Erdheim-Chester disease: a systematic review. Crit Rev Oncol Hematol 2015;95:1–11.
[73] Monsereenusorn C, Rodriguez-Galindo C. Clinical characteristics and treatment of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 2015;29:853–73.
[74] Strowd RE, Burger P, Holdhoff M, Kleinberg L, Okun MS, Olivi A, et al. Steroid-responsive intracranial germinoma presenting as Holmes' tremor: importance of a tissue diagnosis. J Clin Neurosci 2015;22:911–3.
[75] Si SJ, Khatua S, Dhall G, Nelson MD, Gonzalez-Gomez I, Finlay JL. Regression of primary central nervous system germinoma after dexamethasone administration: a case report. Pediatr Hematol Oncol 2010;27:237–43.
[76] Mascalchi M, Roncaroli F, Salvi F, Frank G. Transient regression of an intracranial germ cell tumour after intravenous steroid administration: a case report. J Neurol Neurosurg Psychiatry 1998;64:670–2.
[77] Konno S, Oka H, Utsuki S, Kondou K, Tanaka S, Fujii K, et al. Germinoma with a granulomatous reaction. Problems of differential diagnosis. Clin Neuropathol 2002;21:248–51.
[78] Endo T, Kumabe T, Ikeda H, Shirane R, Yoshimoto T. Neurohypophyseal germinoma histologically misidentified as granulomatous hypophysitis. Acta Neurochir 2002;144:1233–7.
[79] Catford S, Wang YY, Wong R. Pituitary stalk lesions: systematic review and clinical guidance. Clin Endocrinol 2016;85:507–21.
[80] Sotoudeh H, Yazdi HR. A review on dural tail sign. World J Radiol 2010;2:188–92.
[81] Honegger J, Buchfelder M, Schlaffer S, Droste M, Werner S, Strasburger C, et al. Pituitary working group of the German Society of Endocrinology: treatment of primary hypophysitis in Germany. J Clin Endocrinol Metab 2015;100:3460–9.
[82] Fukuoka H. Hypophysitis. Endocrinol Metab Clin N Am 2015;44:143–9.
[83] Bellastella A, Bizzarro A, Coronella C, Bellastella G, Sinisi AA, De Bellis A. Lymphocytic hypophysitis: a rare or underestimated disease? Eur J Endocrinol 2003;149:363–76.
[84] Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune hypophysitis. Endocr Rev 2005;26:599–614.
[85] Leow MK, Kwek DS, Ng AW, Ong KC, Kaw GJ, Lee LS. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin Endocrinol 2005;63:197–202.
[86] Shimatsu A, Oki Y, Fujisawa I, Sano T. Pituitary and stalk lesions (infundibulo-hypophysitis) associated with immunoglobulin G4-related systemic disease: an emerging clinical entity. Endocr J 2009;56:1033–41.
[87] Bellastella G, Maiorino MI, Bizzarro A, Giugliano D, Esposito K, Bellastella A, et al. Revisitation of autoimmune hypophysitis: knowledge and uncertainties on pathophysiological and clinical aspects. Pituitary 2016;19:625–42.
[88] Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016;101:3888–921.
[89] De Bellis A, Colao A, Pivonello R, Savoia A, Battaglia M, Ruocco G, et al. Antipituitary antibodies in idiopathic hyperprolactinemic patients. Ann N Y Acad Sci 2007;1107:129–35.
[90] Shelly S, Boaz M, Orbach H. Prolactin and autoimmunity. Autoimmun Rev 2012;11:465–70.
[91] De Bellis A, Bizzarro A, Bellastella A. Role of prolactin in autoimmune diseases handbook of systemic autoimmune diseases series. In: Asherson RA, Walker S, Jara LJ, editors. Endocrine Manifestations of Systemic Autoimmune Diseases. 9. 2008. p. 23–9.
[92] Larouche V, Correa JA, Cassidy P, Beauregard C, Garfield N, Rivera J. Prevalence of autoimmune disease in patients with prolactinomas and non-functioning pituitary adenomas. Pituitary 2016;19:202–9.
[93] Sugihara Hitoshi. Review on recent topics in hypophysitis. J Nippon Med Sch 2017;84:201–8.
[94] Ray DK, Yen CP, Vance ML, Laws ER, Lopes B, Sheehan JP. Gamma knife surgery for lymphocytic hypophysitis. J Neurosurg 2010;112:118–21.
[95] Selch MT, DeSalles AA, Kelly DF, Frighetto L, Vinters HV, Cabatan-Awang C, et al. Stereotactic radiotherapy for the treatment of lymphocytic hypophysitis. Report of two cases. J Neurosurg 2003;99:591–6.