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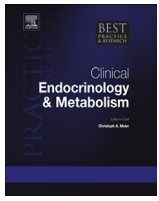

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# Thyroid gland and brain: Enigma of Hashimoto's encephalopathy

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The versatile clinical manifestations of the Hashimoto's chronic autoimmune thyroiditis often include psycho-neurological disorders. Although hypothyroidism disturbs significantly the ontogenesis and functions of central nervous system, causing in severe cases of myxedema profound impairment of cognitive abilities and even psychosis, the behavioral, motor and other psychoneurological disorders accompany euthyroid and slightly hypothyroid cases and periods of Hashimoto's disease as well, thus constituting the picture of so called “Hashimoto's encephalopathy”. The entity, although discussed and explored for more than 50 years since its initial descriptions, remains an enigma of thyroidology and psychiatry, because its etiology and pathogenesis are obscure. The paper describes the development of current views on the role of thyroid in ontogeny and functions of brain, as well as classical and newest ideas on the etiology and pathogenesis of Hashimot's encephalopathy. The synopsis of the world case reports and research literature on this disorder is added with authors' own results obtained by study of 17 cases of Hashimoto's thyroiditis with schizophrenia-like clinical manifestations. The relation of the disease to adjuvant-like etiological factors is discussed. Three major mechanistic concepts of Hashimoto's encephalopathy are detailed, namely cerebral vasculitis theory, hormone dysregulation theory and concept, explaining the disease *via* direct action of the autoantibodies against various thyroid (thyroperoxidase, thyroglobulin,

*Abbreviations: aTPO*, autoantibodies against thyroid peroxidase; *aNAE*, autoantibodies against N-terminal of α-enolase; *CNS*, central nervous system; IVIG, intravenous (human polyclonal) immunoglobulins; *HE*, Hashimoto's encephalopathy; *MOG*, myelin-oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; *SREAT*, steroid-responsive (-reactive) encephalopathy in autoimmune thyroiditis.

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and TSH-receptor) and several extrathyroid antigens (alpha-enolase and other enzymes, gangliosides and MOG-protein, onconeuronal antigens) – all of them expressed in the brain. The article demonstrates that all above mentioned concepts intermingle and prone to unification, suggesting the unified scheme of pathogenesis for the Hashimoto's encephalopathy. The clinical manifestations, criteria, forms, course, treatment and prognosis of Hashimoto's encephalopathy and its comorbidity to other diseases – are also discussed in brief. The relation between Hashimoto's encephalopathy and non-vasculitis autoimmune encephalomyelitides of paraneoplastic and non-paraneoplastic origin is emphasized [1 figure, bibliography – 200 references].



## Thyroid regulation is essential for ontogenesis and functions of central nervous system

The thyroid hormones are crucial for normal development and function of central nervous system (CNS), which was first suspected as early as in XIX century, when clinical manifestations of myxedema were described. The synopsis of pioneering studies in this field is given elsewhere [1]. Nowadays it is common knowledge that the mechanisms of memory and learning are based on the plasticity of the CNS synaptic structures, provided, in particular, by the changes in the neuronal biosynthesis of RNA and proteins, which are involved in the potentiation of synaptic transmission [2–5]. The resulting patterns of long-term strengthening of connections between neurons create a structural and functional correlate of experience or, in the terms of K.H. Pribram [2], a “memory engram”. Even in the early period of studying memory mechanisms, thyroid hormones attracted attention, and not only because of clinical observations about learning disabilities in state of hypothyroidism and accelerated associative thinking in opposite state of hyperthyroidism. Graves' disease often causes obvious neuropsychiatric syndrome, decreasing the quality of life in such patients because of their extreme tachyphrenia [6]. A phenomenon known for a long time is the long-term dependence of the synaptic transmission potentiation on ribosomal translation, as well as the ability of thyroid hormones to increase the activity of amino-acyl-t-RNA synthetases for almost all amino acids in different organs and tissues, reducing it in the atrophic organs during metamorphosis [7,8]. Subsequent studies showed that the production of neurotrophic factors depends on thyroid hormones, and is impaired in the hippocampus, cerebellum and cerebral cortex during hypothyroidism. The injection of thyroid hormones partially reverses the changes caused by hypothyroidism as regards to the brain organogenesis and functioning of learning and memory mechanisms [9–13]. Thyroid hormones, along with retinoids, are now recognized as key signals regulating neuronal plasticity associated with learning, and changes in the expression of transthyretin (blood carrier of these bio-regulators) serve as a characteristic correlate of memory traces consolidation [5]. It has been demonstrated that phagocytic behavior of microglia in rat brain also is thyroid-depending [14]. The reduction of neuronal networks essential for maturation of brain as well as programmed cell death in the brain – both are based on thyroid–depending apoptotic processes [15]. Hence, violation of the programmed formation of neural populations during brain development may be one of the main causes of early hypothyroid dementia. Interestingly, thyroid hormones also control apoptosis of lymphocytes, which explains lymphocytosis observed in hypothyroid disorders, including Hashimoto's thyroiditis [16]. In plus thyroid hormones *via* activation of $K^+$-$Na^+$ –ATPase may accelerate bioelectric processes in all excitable tissues, including nervous one [17]. These aspects of thyroid action are relevant for both the developing and adult brains, not necessarily in status of iodine deficiency, but also during brain regeneration after injuries, as well as under hypothyroidism caused by other reasons, like lead poisoning [13,18–20]. Thyroid hormones control the fate of brain stem cells [21]. Thus, thyroid insufficiency in the embryonic and early fetal periods causes a delay in the differentiation of the cerebral cortex at the critical stage of its formation and inhibition of

the development of the psyche, which is manifested in Fagge's disease, an early form of hypothyroidism with profound mental retardation down to imbecilic state and severely impaired emotional sphere [1]. For many decades, the problem of hypothyroid cretinism was associated in medicine mostly, if not exclusively, with iodine deficiency [22].

However, nowadays the most prevalent autoimmune disease in humans is Hashimoto's chronic autoimmune thyroiditis. Moreover, if untreated and advanced, it is actually the leading cause of hypothyroidism worldwide, at least in waste territories with sufficient/excessive iodine supply [23,24]. Excess of iodine is one of the risk factors for this autoimmune disorder because of adjuvant-like effects of this trace element on the different cells of immune system [24–27] and due to adaptive alternative splicing of thyroglobulin and thyroid peroxidase caused by sharp fluctuations of iodine supply, which may result in non-tolerized state of lymphocytes that meet such antigenic variants of these proteins [28].

The clinical manifestations of hypothyroidism are very diverse. They obligatory include psychoneurological disorders. In 1949 British medical scholar Richard Asher gave a classic description of the syndrome that he called “Myxedematous madness” in an article titled with the same name, and associated psychic disorder with hypothyroidism. He described 14 clinical cases and accentuated some symptoms, like general tiredness, gain in weight, vague aching pains in the legs, poor memory, constipation, hearing loss, alopecia, dry skin, cold intolerance, changes of voice, and mental/physical slowness [29]. Curiously, even earlier (1937) a bright description of hypothyroid madness in a Welsh miner, successfully treated with thyroid extract, gave an outstanding Scottish novelist and truant physician Archibald Joseph Cronin in his fiction novel “The Citadel” [30].

Currently psychiatrists recognize that hypothyroidism is obvious background for mood disorders, changes of behavior and decrease of cognitive abilities, emphasizing in its clinical manifestation such symptoms as: Slowing down and inhibition of the higher nervous activity, tardiness and perseveration of thinking and speech, memory loss, failure of skills and abilities, adynamia and akinesia. The last manifestation sometimes resembles a stupor, accompanied with asthenic syndrome and a picture of organic dementia [31]. Hypothyroidism accelerates the development of neurodegenerative diseases which result in dementia, including Alzheimer disease [32,33]. Interestingly, tau-protein, a marker of the last disorder, is expressed in buccal epithelium of autoimmune thyroiditis patients without diagnosed Alzheimer disease [34]. It is known that patients in overt clinical hypothyroidism may have anxiety, failures in attention, orientation, learning, and perception, decrements in general intelligence, language, psychomotor and executive functions [35–37]. Some serious psychic disorders like paranoid delusions, depression and confusional states are also common in myxedema [38]. Thyroid status is essential for normal organogenesis of cerebellum, including growth and arborization of the Purkinje neurons, as well as for myelination and synaptogenesis in this part of brain, which is important for understanding cerebellar impairment in thyroid diseases [39].

## Brain manifestations of Hashimoto's disease are not merely results of hypothyroidism

In 2002, a group of scientists from Norway failed to find any statistically significant association between thyroid hormone levels and the presence of depression or anxiety disorder in a large, unselected population [40]. The point is that bright hypothyroidism occurs in advanced stage of Hashimoto's disease only. The course of chronic autoimmune thyroiditis may include long euthyroid periods of compensation and even display hyperthyroid episodes caused by thyroid hormone efflux from demolishing thyrocytes as well as by parallel effects of anti-TSH-receptor agonistic autoantibodies. The last phenomenon is inherent to quite common cases of *hashitoxicosis* or twinned Hashimoto's disease, with its cellular autoimmunity towards thyroid gland, and Graves' disease depending on humoral anti-receptor autoimmunity [23–25].

In context of present article, the most essential detail is that psychic disorders in Hashimoto's thyroiditis may occur *not only in overt hypothyroidism, but also in slight or subclinical one* [40,41] or even in *euthyroid status of the patients* [41–44]. This observation provokes a suggestion that not merely lack of thyroid hormones, but also impact of some other factors – let say, autoimmune ones – may be involved in pathogenesis of brain disorders among Hashimoto's thyroiditis patients.

## Hashimoto's encephalopathy: birth of the term

The first association between Hashimoto's thyroiditis and CNS disorder ever mentioned was the presence of symptoms interpreted as cerebellum impairment. In 1960, E.H. Jellinek and R.E. Kelly described six cases of cerebellar involvement in myxedema and emphasized that in their cases (and in few earliest similar descriptions they referred to) cerebellar disorders sometimes preceded advanced myxedema [45]. In 1961 S. Nickel and B. Frame tried to analyze the neuromuscular manifestations of myxedema. They revealed broad variety of them, including gait disorders, convulsions, and cranial nerve involvement. The cerebellar syndrome in myxedema usually but not always could be improved by replacement therapy. In addition, paresthesia, sensory loss, and muscle weakness they considered to be part of myxoedematous neuropathy and myopathy [46]. Later E.H. Jellinek and K. Ball, in co-authorship with eminent neurologist Lord W. Russel Brain for the first time coined a probable new nosological entity, which they called "Hashimoto's encephalopathy" (HE). It was a case of a 48 years old man with proven Hashimoto's thyroiditis, treated with thyroxine, who experienced 12 attacks of psycho-neurological disorder during 17 months, being for major part of this period in *euthyroid state*. The symptoms were hemidysesthesias, aphasia, hemiplegia, hemianopsia, confusion, paresthesias, periods of agitation and depression, tremor, hallucinations and even stupor. The disorder ended with a spontaneous relief. The eponym HE *per se* is quite doubtful, because Hakaru Hashimoto, who first described chronic autoimmune thyroiditis under the name "struma lymphomatosa" in four Japanese females (1912), did not mention in his single original paper any signs of their encephalopathy [48]. HE was considered by authors a rare neuroendocrine syndrome, perhaps an autoimmune disease of the brain. It is also known as *steroid-reactive (or steroid-responsive) encephalopathy, associated with autoimmune thyroiditis* (SREAT). When trying to treat HE with glucocorticoids, in most cases a significant positive effect was achieved. *Ex juvantibus* it witness for the inflammatory nature of HE cerebral symptoms [49,50].

## Clinical manifestations of HE

HE has a variety of clinical symptoms that mimic an assortment of neurological and psychiatric disorders. Most frequently, psycho-neurological manifestations appear as cognitive dysfunction (36–100%), tremor (28–84%), altered consciousness (26–85%), transient aphasia (73%–84%), seizures (52–66%), myoclonus (37–65%), gait disorder/ataxia (28–65%), and focal deficit (27–67%). Stroke-like episodes are common (18–31%). In 12–20% of cases, epileptic status (as a rule resistant to common antiepileptic drugs) was diagnosed [51–55], although recent study did not find any difference in clinical, laboratory and instrumental data of those HE patients who did develop epileptic status and those who did not [56]. Psychotic disorders can manifest themselves in the form of paranoid, visual hallucinations, and mood disturbances. Even bright oneiroid syndrome, delirious manias and catatonia were described [55,57–59]. Hashimoto's thyroiditis is related to significant increase in frequency of phobic and obsessive episodes, compared to control group [60]. All together diagnosis of psychosis was suspected in 25–36% of patients [54]. Two patterns of HE, although not strictly delineated, are known, one displayed in the episodic attacks with predominance of stroke-like and focal symptoms, like in disorders of cerebral circulation, versus alternative one characteristic for indolent progressive course of cognitive disorder with psychotic manifestations. The motor disorders, like seizures, myoclonus and tremor are common in both variants [55]. The role of cerebellar manifestations in HE (manifested with hypotonia, opsoclonus, dysmetria, and dysdiadochokinesia) was noticed long ago, but is still emphasized [61].

Although many researchers are sure that HE, since it is steroid-sensitive, can be regarded as an inflammatory autoimmune disorder, both its precise etiology and pathogenesis are still unclear. It is not even agreed whether HE represents encephalitis or cerebral vasculitis. Moreover, there is also a number of steroid-resistant cases of HE [62].

## Epidemiology, etiology and co-morbidity

The incidence of HE is estimated as 2.1/100 000 [54] with 85% of female cases, although several most severe ones are described in males [55]. Few possible risk factors mentioned in various case reports were the effects of adjuvant-like or immunostimulating agents of exogenous (alpha-interferon, Epstein-Barr virus) [57,63,64] or endogenous (estrogens) [65,66] origin. Lithium which produces TSH resistance of thyrocytes was accused as one more provocation factor for HE [67]. The disease is most typical for female patients of middle age (40–50 years old), although considerable number of pediatric cases was described (beginning from 14 months old kid, but most of early cases observed during menarche period of adolescent girls), as well as few geriatric ones are – up to a 86 years old woman [53–55,68–71].

The majority of HE patients were euthyroid or slightly hypothyroid to the moment of its first appearance, but several deeply hypothyroid and even obvious hyperthyroid cases with Graves' disease also were reported [53,59,72–74]. In more than one third of observations there was comorbidity of HE with other systemic and/or organ specific autoimmune diseases, most typically with lupus, Sjogren's syndrome, atrophic gastritis/pernicious anemia and myasthenia gravis, but also with many others, like sarcoidosis and autoimmune hypophysitis [75–78]. It has been clearly demonstrated that Hashimoto's thyroiditis *per se* very often occurs in co-morbidity with rheumatological and other autoimmune and immunopathological disorders [24,79,80]. There is a case of HE associated with rapid development of narcolepsy, a syndrome which now is also proven to have in some cases autoimmune origin [81].

To our opinion, the most remarkable co-morbidity of HE is an association with peripheral polyneuropathies, involving sensory and autonomic nerves, observed in a case of an adolescent girl [82]. Polyneuropathies, especially those altering small neural fibers are now considered to be common manifestations of many autoimmune or suspiciously autoimmune syndromes [83]. There was reported another case of HE paralleled with the symptoms of sensory ganglionopathy or patchy involvement of sensory nerves, also peculiar to some other autoimmunopathies [84].

## Laboratory data and role of anti-thyroperoxidase autoantibodies

The electroencephalogram in HE is quite non-specific and may depict a regional slowdown of the frontal intermittent rhythmic delta activity, three-phase waves, sometimes epileptiform activity, photoparoxysmal and photomyogenic phenomena. In more than 90% of cases, intermittent slow-wave activity is noted [50]. The presence of elevated titers of anti-thyroperoxidase autoantibodies (aTPO) is mentioned as one of criteria for the diagnosis of HE [51], because aTPO blood level is increased in 95–100% of HE cases. There were also data about presence of aTPO in cerebrospinal fluid of HE patients due to their possible intrathecal production [85]. Anti-thyroglobulin autoantibodies, observed in elevated serum concentrations in 73% of HE cases [55] also were discovered in cerebrospinal fluid [86]. The liquor of HE patients commonly has increased concentrations of protein, namely immunoglobulins [51,52]. Some authors reported increased level of $IgG_4$ in cerebrospinal fluid of HE patients [87]. Cerebrospinal fluid of several HE patients contained a marker of neuronal destruction [88,89]. There were revealed lymphocytic pleocytosis [90] and even oligoclonal immunoglobulin bands on its electrophoregrams [55]. However, the real impact of the serum and liquor autoantibodies towards thyroid antigens into HE pathogenesis is unclear; moreover, in early period of HE studies many authors considered them to be innocent bystanders and looked for alternative pathogenetic mechanisms. The reason is simple: Autoantibodies of these thyroid specificities are quite common in many autoimmune diseases not accompanied with HE and even occur in 2–20% of healthy individuals, although in low titers, with a tendency to increase with age [49,55]. To date, no clear relationship has been established between the features of the clinical picture and the type/level of antibodies present in HE, exactly like it was not precisely determined also for Hashimoto's thyroiditis itself [24]. Many researchers consider that the increase in the level of anti-thyroid autoantibodies is proportional to the activity of the disease, and after treatment with corticosteroids, their level decreases [49].

## Pathogenesis: Vascular theory

Three major mechanisms were suspected in pathogenesis of HE: vasculitis-related, autoantibody-related (including those against not only thyroid, but also extrathyroid antigens) and finally a mechanism related to toxic/deregulatory influence of some hormones, excessively produced in response to hypothyroidism.

Initially HE was interpreted as a kind of immunopathological vasculitis, maybe of immune complex origin, altering the brain microvasculature and producing local oedemata. Jellinek et al. [47,91] coined such an assumption in the first papers on this nosological entity. The single proof for that was a presence of hypoperfusion zones on brain computed tomographic images in some of the cases [69,85,91–94], especially during mental exercise tests [95].

However, other authors did not reveal any focal or diffuse changes typical for hypoperfusion or microinfarctions in HE patients by brain imaging techniques, just confirming progressive symmetric atrophy of their gray matter [93], or revealed normal brain angiographic images [96]. Hashimoto's thyroiditis if not treated may cause hypothyroid acceleration of atherosclerosis and early complicated metabolic syndrome with precocious aging, thus leading to dangerous complications and life shortening [24]. Unfortunately, because of long time elapsing between the beginning of non-recognized disease and these outcomes, such a connection is still underestimated among diagnostic pathologists. Hence, the disease habitually is not considered in health care as potential cause of death, and due to this thyroid gland is very rarely subjected to special examination on routine autopsies. Also, the brain of HE patients was quite rare available for post mortem pathomorphological studies – just in few cases: like in suicides, in very old deceased patients for differentiation with neurodegenerative diseases, or after lethal epileptic attacks [92,93,96,97]. Nevertheless, in such cases several authors documented presence of vasculitis (phlebitis or polyangiitis) through all the brain or at least in the brainstem of HE victims [93,96–99]. Small and medium-sized blood vessels or perivascular spaces were infiltrated with lymphocytes, predominantly of T-subsets [98,100]. These and similar findings brought by rare brain biopsies substantiated a concept interpreting HE as a brainstem vasculitis (angiitis) caused by immune complexes and/or lymphocytic infiltration of vascular walls [101–103].

## Are the “thyroid” antigens organ-specific?

Of course, another pillar, supporting the vasculitis theory of HE, was a necessity to explain in some way relation of HE to the increase of aTPO titers, in spite of existed for some period viewpoint insisting that thyroperoxidase is exclusively thyroid antigen. The real degree of tissue specificity of thyroid antigens has been re-evaluated. One time not only thyroperoxidase was considered an organ-specific enzyme. Similarly, another thyroid antigen – thyroglobulin – also was believed to be a marker of thyrocytes. Nowadays it is common knowledge that there exists a family of peroxidases (thyroid peroxidase, myeloperoxidase from neutrophils, eosinophil peroxidase and peroxidase expressed by vascular endothelium) with a considerable homology between them [104–106]. There was a study showing that aTPO do not recognize epitopes of myeloperoxidase [107], yet there were cases of Wegener's granulomatosis with polyangiitis comorbid with HE [108]. Moreover, thyroglobulin and TSH receptor are also not unique for thyroid, being expressed by fibrocytes of retro-orbital fat [109]. Many other cells in bone, kidney, heart, and intestines, as well as adipocytes and lymphocytes – all possess with TSH receptors [110]. For the pathogenesis of HE it is especially important that all major thyroid antigens altered in autoimmune thyroid disease definitely are expressed in human brain. Anti-thyroglobulin autoantibodies recognize antigens of cerebral vasculature, anti-TSH-receptor autoantibodies bind to cortical neurons, and aTPO localize on astroglial cells of cerebellum and cerebral cortex [111–113]. It means that extrathyroid symptoms of Hashimoto's disease which involve CNS can be mediated *via* anti-thyroid autoantibodies. Also it puts closer vasculitis concept of HE and anti-brain autoantibody concept, because HE vasculitis in brain can be mediated not necessarily *via* immune complexes, but *via* cytotoxic effects triggered by autoantibodies against targets shared by thyrocytes and endothelium.

## Pathogenesis: Hormone-related concept is still alive

Prior to discussion of the other possible targets of autoimmunity against CNS of HE patients, it is worth to pay attention to hormonal dysregulation theory of its pathogenesis. The thyrostate is a subject of servomechanisms establishing the increase in hypothalamic thyroliberin and pituitary TSH secretion in response to hypothyroidism. But, thyroliberin is not just tripeptide, having single hypophysiotropic effect, related to the stimulation of TSH release. It has a complex action over several metabolic and physiological processes, e.g. among other effects it is helpful in depression, cerebellar degeneration (which has many common symptoms with HE) and metabolic aging [114]. The remarkable effect is its prolactoliberin action, actually it is one of the strongest among all stimulators of the prolactin secretion [115–117]. Owing to this effect of thyroliberin, any kind of hypothyroidism even compensated or "subclinical", almost inevitably causes a hyperprolactinemia [24,118,119]. But this is essential for pathogenesis of infertility in Hashimoto's thyroiditis and serves as a vicious circle for the self-perpetuating mechanism of autoimmunity in this disease, due to adjuvant-like action of prolactin on immune system [24,120].

Another set of thyroliberin effects is related to motor disorders: Its excess provokes tremor, seizures and even epileptic activity [121]. However, such motor manifestations are very common in HE. Hyperprolactinemia *per se* also can cause some psychic disorders. That is why back in 1980ies the French scholars coined the idea of thyroliberin-depending character of the HE symptoms [122–124]. Successful treatment of some HE cases without glucocorticoids, just with thyroxine, as well as exacerbations of HE in luteal phase of menstrual cycle also witnessed for possible roles of thyroliberin and/or prolactin excess in its mechanisms [121]. Due to this, a group of Japanese physicians performed clinical experimental study of the effects of thyroliberin in a HE patient with relapses related to lutheal phase of menstrual cycle. They measured TSH and prolactin blood levels after thyroliberin injection [125]. The results were controversial. Thyroliberin injections in dose-depending manner provoked motor disorders typical for HE exacerbations in this patient, but although TSH levels increased, prolactin concentrations did not display similar growth. Because many non-immunopathological cases of hypothyroidism are not complicated with HE, it seems unlikely that hormonal impairments alone are able to establish its development. Up to 35% of patients with HE have subclinical hypothyroidism and 20% have obvious hypothyroidism, but 30–40% are euthyroid, and 10% are in hyperthyroid status [52,53], so their hormonal spectrum cannot be identical, in spite of the same diagnosis. However, we do not consider obsolete hormonal (or using authentic terminology – "toxic") theory of HE. It may be linked to autoimmune concepts, because hyperprolactinemia is a proven risk factor of autoimmunity [120]. Moreover, thyroxine therapy in Hashimoto's disease is not just a replacement treatment, but also rather immune modulating one. The point is that thyroid hormones, as it was mentioned above, are able to induce apoptosis of lymphoid clones [16]. In plus they also decrease the level of prolactin by withdrawal of thyroliberin/prolactoliberin effects. Because of that, thyroxine treatment not only influences hormonal status of autoimmune thyroiditis patient, but also decreases the titers of antithyroid and other (for example, anti-platelet) autoantibodies in Hashimoto's disease, and their effect sometimes is comparable to that of glucocorticoids [126]. The neuroleptics, known for their hyperprolactinemic influence, may cause exacerbations of HE [127]. For the hyperthyroid cases of HE the Japanese authors postulated possible toxic role of 3-iodothyronine [74], which is known to penetrate into brain and stimulate proinflammatory and phagocytic behavior of microglial cells [14]. Presumably, this effect can promote autoimmune/inflammatory processes in CNS of such patients [74].

Hence, pathogenesis of HE may consist of intermingled mosaic embedding the immunopathological brain vasculitis, dyshormonal pro-autoimmune and pro-psycho-neuropathogenic changes along with the probable direct effects of autoantibodies (Fig. 1).

## Various autoantibodies in pathogenesis of HE

Nevertheless, what kind of autoantibodies is most essential for HE? For sure, these are not only antithyroid immunoglobulins mentioned above, like aTPO. There are evidences of a relationship between HE and many other autoantibodies towards enolases, dimethylargininase-I (aka: 36 kDa cortical antigenic protein), aldehyde reductase-I, myelin-oligodendrocyte glycoprotein, gangliosides and few

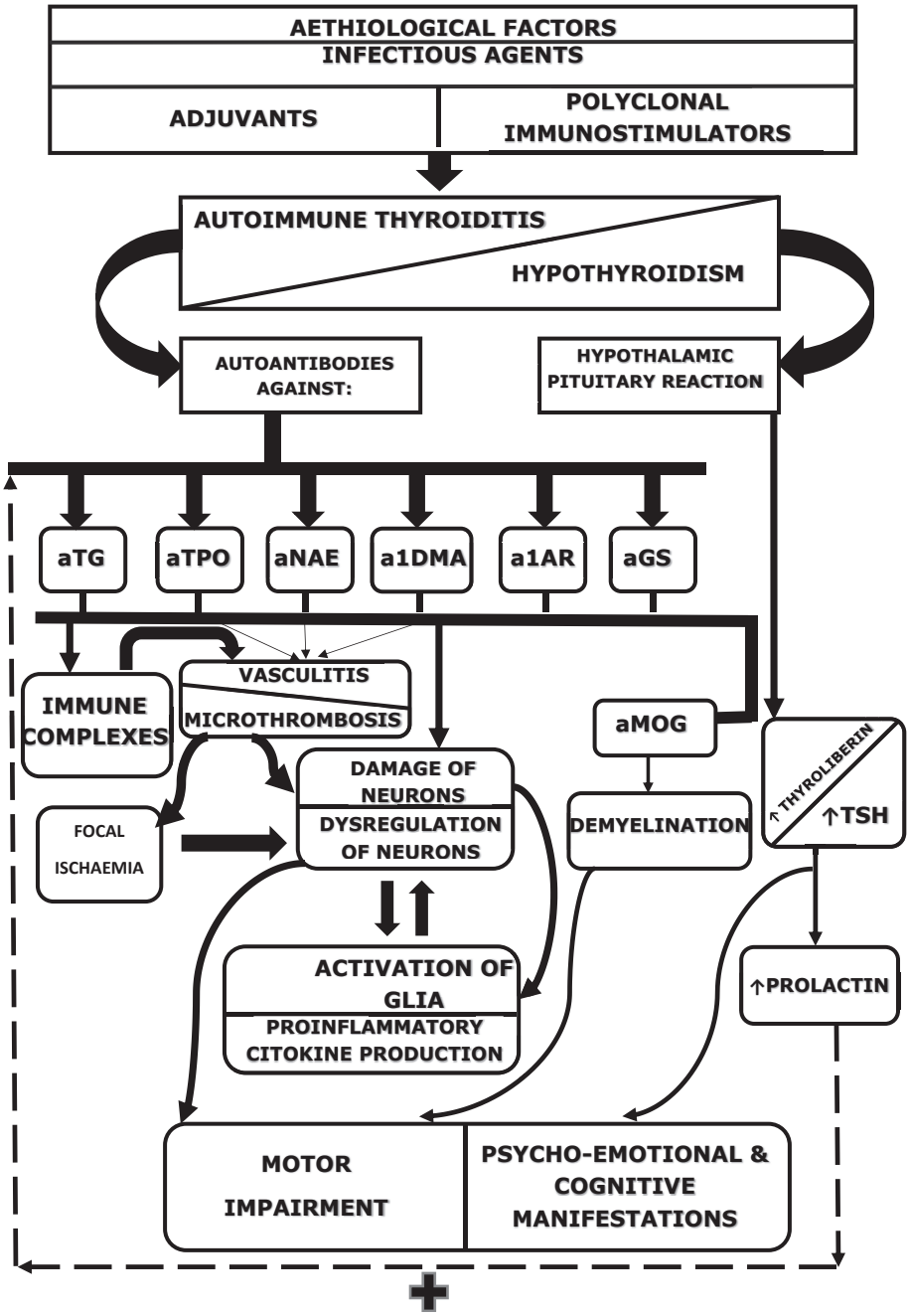


**Fig. 1.** Scheme of pathogenesis of HE. ABBREVIATIONS: a1AR – autoantibodies against 1-aldoreductase, a1DMA –autoantibodies against 1-dimethylarginase, aGS – anti-ganglioside autoantibodies, aMOG – autoantibodies against myelin-oligodendrocyte glycoprotein, aNAE – autoantibodies against N-terminal peptide of alfa-enolase, aTG – autoantibodies against thyroglobulin, aTPO – autoantibodies against thyroid peroxidase, HE – Hashimoto's encephalopathy TSH – thyroid stimulating hormone.

onconeuronal antigens (see below). There are observations of the pathogenetic contribution of such autoantibodies in encephalomyelitis of HE patients. HE-like manifestations are observed in autoimmune paraneoplastic encephalitides [55,128]. For the practitioners the differential diagnosis of autoimmune encephalitis with "true HE" looks quite actual task [55,69], but for the pathophysiologists the similarity of these entities is much more important because it may reflect common pathways of their pathogenesis. Hans Selye's well-known thrope about physicians who are interested mostly in differences between diseases and pathologists, who are concentrated on their similarity or common tiles is entirely applicable to HE [129].

*Anti-enolase autoantibodies*

The most promising finding of last decades, as regards to the spectrum of autoimmunity in HE, was a reveal of autoantibodies towards N-terminal of alpha-enolase (aNAE) in many cases of this disorder. The Japanese authors first reported the high incidence of seropositivity for aNAE in HE (60–83%) and later also demonstrated the role of this autoantigen in HE by means of proteome analysis [130–133]. Recently aNAE were revealed also in combined case of HE and dementia with Lewy bodies [134]. Brain magnetic resonance imaging (MRI) revealed in HE patients positive for aNAE diffuse non-specific white matter abnormalities and multiple small subcortical limbic lesions worsened in relapses and improved after recovery [135].

The target enzyme, 48 kD protein – 2-phospho-D-glycerate hydrolase, is evolutionary highly conservative and essential catalyst of glycolysis, broadly represented in various cells of human organism as well as in many bacteria and fungi, e.g. Candida [136,137]. This allures to assume that cross-reactivity between certain microbial epitopes and human α-enolase can induce aNAE autoimmunity. Similar mechanism was hypothesized for a case of post-treatment Lyme disease chronic fatigue syndrome with autoantibodies towards γ-enolase, and shared sequences were located in human and Borrelia burgdorferi homologous enzymes [138]. The cross-reactivity of α-enolases from Streptococci and human cells is involved in pathogenesis of rheumatic fever [139] and perhaps several other infectious diseases [140].

The α-enolase is expressed not only in brain vasculature (and in embryonic neurons also), but in many (if not all) cells through the body [136,137]. The isomer of this enzyme, γ-enolase, traditionally called "neuron-specific" in fact is by far not exclusive for neurons and expressed in many cells of paraneuronal origin, which belong to disperse neuroendocrine system – and even in some other cells. It is expressed among others in pituitary and C-cells of thyroid gland [136,141–143]. Both mentioned enolases are highly homologous and even have epitopes, which are recognized by same or similar autoantibodies, for example in autoimmune hypophysitis [143]. Some tumors (including thyroid cancer from parafollicular C-cells) express increased amounts of enolases, which gives them metabolic advantages in competition with normal host cells. Also, it has common C-terminal with a tumor promoter MBP-I [136,140–142,144]. Due to this, it is possible that increase in aNAE autoreactivity is a paraneoplastic phenomenon, caused by an attempt of immune system to hit the essential element of cancer cell vitality [137,144], and hence NAE-positive HE cases may be interpreted as a kind of paraneoplastic autoimmune encephalitis with antibodies against onconeuronal antigens, for example in thyroid cancer (including its earliest indolent in situ stages). Besides parafollicular thyroid cancer, the level of aNAE increases in several other cancer diseases: Pancreatic, buccal-gingival, liver, breast, uterine cervix, renal and lung tumors, sometimes associated with paraneoplastic autoimmune disorders [137,141,142,144,145]. The levels of autoantibodies towards α-, γ-, or both enolases – are increased in sera of patients not only in HE, but in great number of various autoimmune diseases, especially those manifested with systemic vasculitides: lupus, reumatoid arthritis, ANCA-positive vasculitides, immunopathological nephritis, as well as in scleroderma, Sjoghen's syndrome, paraneoplastic autoimmune retinopathy and optic neuritis, autoimmune hepatitis, cholangitis, primary biliary cirrhosis, inflammatory bowel and celiac diseases, relapsing chondritis, ovarian failure, endometriosis and all types of autoimmune hypophysitis [137,140,141,143–145]. Another intriguing feature of α-enolase is its ability to bind plasminogen with high affinity. The effect is used by the microorganisms for their adhesiveness and, probably, can be altered by aNAE [136,137,140]. By the analogy with pathogenesis of antiphospholipid syndrome [146], autoimmunity to receptor protein interfering noticeably in

coagulation/anticoagulation mechanisms [147] most probably is able to cause vascular complications, including those responsible for HE brain hypoperfusion [55,102]. Interestingly, γ-enolase is expressed also by human platelets [148], which fact makes the above said speculations stronger, because autoantibodies towards platelet antigens and even immune thrombocytopenic purpura are not infrequent in Hashimoto's thyroiditis [24,149,150]. There was described even multiple autoimmune combination of Hashimoto's disease, cerebral vasculitis and thrombocytopenic purpura [151]. The aNAE are typical for recurrent miscarriages, as well as some autoantibodies peculiar to antiphospholipid syndrome [152], which may witness for possible common mechanistic links of both autoimmunopathies. Hashimoto's thyroiditis has intermingled co-morbidity with antiphospholipid syndrome and may cause miscarriages, obviously not only because of accompanying hyperprolactinemia [24,153,154]. The autoantibodies to α-enolase produce apoptosis of endotheliocytes, thus facilitating microcirculatory disorders embedded in HE pathogenesis [137,140,155,156]. The α-enolase is expressed on the surface of lymphoid as well as mononuclear blood and synovial cells, and their bound to these targets may increase production of potent pro-inflammatory cytokines by the involved cells, which is coined as probable additional pathogenetic mechanism for rheumatoid arthritis [137,157] and maybe also for HE. T. Leyhe and K. Müssig made the last assumption in 2014 [158]. In autoimmune thyroiditis production and systemic concentrations of several proinflammatory cytokines, including monocyte chemoattractant protein-1, interferon-γ, leptin and tumor necrosis factor-α increase, and the levels of their anti-inflammatory counterparts (Interleukin-10, adiponectin) fall down [23–25,158]. Of course, this does not mean that similar changes characterize both the local paracrine and systemic endocrine concentrations of this topically acting autacoids. However, authors [158] emphasized that pro-inflammatory cytokines adversely affect metabolism of multiple neurotransmitters, such as serotonin, dopamine and glutamate, disrupting their biosynthesis, release and reuptake, which may lead to changes in various brain neuronal circuits and present important additional link in pathogenesis of HE. In addition, it has been demonstrated that pro-inflammatory cytokines are able to stimulate the production of chemokines by the thyrocytes themselves [159], thus closing a vicious circle in pathogenesis of autoimmune thyroid diseases. The aNAE production in HE is related to steroid sensitivity of the disease [76,131–134]. In several other autoimmune diseases, their production appeared to be most characteristic for carriers of HLADR8 allele and provoked by cross-reacting yeast antigens. The citrullinated modification of the enolases is most probable target of autoimmunity [160]. Nevertheless, aNAE are absent in 40%–50% of HE patients, who were checked for them [129,161], which means that they alone cannot be responsible for the whole picture of this disease. In 10% of autoimmune thyroiditis patients without HE the aNAE were also registered [131]. Moreover, low titers of similar anti-brain autoantibodies of various specificities are quite common in the majority of healthy donors, thus proving that their reveal *per se* does not yet mean existence of brain disorder [162], but rather could be a feature of natural physiologic autoimmunity, a phenomenon to which regulatory functions are attributed [163].

*Other enzymes as targets of autoimmunity in HE*

Nowadays the list of so called "organ-specific" autoimmune diseases is getting shorter and shorter, because of sensitive advanced laboratory techniques, revealing full spectra of various autoantibodies and owing to the concept of "autoimmunity kaleidoscope" ousting out the previous separation of autoimmune entities on organ-specific and non-specific ones [164]. Multifaceted pathogenesis of HE, most probably, also involves autoantibodies of several different thyroid and extrathyroid specificities, like it happens in Graves' disease, *lupus erythematodes* and few other autoimmune illnesses. In last 2 decades, several authors reported the discovery of various anti-brain autoantibodies in the spectrum of HE autoimmune reactivity in plus to the earlier characterized anti-thyroid and aNAE ones.

Oide T. et al. revealed immunoglobulins of HE patients that recognize a 36 kD-protein in cortical neurons of human and mice brains [161]. Later, this 36-kD antigen appeared to be an enzyme *dimethylargininase-I*, which demonstrated Gini B. et al. [165]. They found in cerebrospinal fluid of six HE patients IgG that recognized two cerebral antigens of neuronal and endothelial location. Another one, with 31 kD of molecular mass was also enzyme – *aldehydereductase-I*, thus giving additional basis for combined vascular-neuronal concept of HE pathogenesis. Later these data were confirmed [166]. The

dimethylarginase-1 is involved in production of endothelial-derived relaxing factor or nitric oxide, thus establishing important vasodilatation signal for functional arterial hyperemia in acting portions of brain. Its failure may be related to regional hypoperfusion on exercises, earlier noticed in HE (see above). The aldehyde reductase-1 activity improves cell survival during reversible necrobiosis, thus functioning as a cytoprotective enzyme for brain. The presence of anti-dimetylarginase-1 autoantibodies was confirmed in HE case related to Hashimoto's thyroiditis comorbid with Down syndrome [166]. Such comorbidity is typical, because Down syndrome very often includes autoimmune thyroiditis [167].

*Non-enzymatic autoantigens in pathogenesis of HE*

In 2008, the first case of HE with autoantibodies against myelin-oligodendrocyte glycoprotein (MOG) was reported in Australia [168]. The authors underlined the common features of clinical and MRI manifestations of HE and various types of encephalomyelitides or neuromyelitis optica in adult and pediatric patients and postulated possible contribution of autoimmune demyelinating process in pathogenesis of HE.

A target of many autoimmune receptor diseases is ganglioside moiety of cell surface receptors, which is responsible for c-AMP-coupling of their signals. It is true also for autoimmune thyroid disease, when autoantibody aimed at ganglioside moiety of TSH-receptor is responsible for major part of hyperfunction, resulting in hyperthyroidism [169]. K. Müssig et al. checked the presence of anti-ganglioside autoantibodies in females with Hashimoto's thyroiditis, and it appeared that anti-ganglioside immunoreactivity is much more typical for this disease, than for other autoimmune thyroid disorders and correlates with cognitive impairment similar to that of HE – even in those cases of Hashimoto's thyroiditis without established HE diagnosis [170].

*HE and autoimmune encephalitides*

The HE displays a considerable overlap of clinical and immunopathological manifestations with a family of autoimmune encephalitides (both of paraneoplastic and non-paraneoplastic origin) caused by anti-receptor and anti-ion channel autoantibodies [55,128]. Among the long list of such encephalitides described in last decade, HE is especially close to different varieties of anti-NMDAR, anti-GABA and anti-AMPAR disorders, sharing with them depressive and hallucinatory symptoms and appropriate autoantibody specificities (towards NR1, NR2b, AMPAR2, GABAAbR etc) [171–173]. Sometimes the differentiation between HE and autoimmune paraneoplastic encephalitides is additionally hardened because lymphoid infiltration in HE may produce on MRI pictures the foci similar to that of tumorous origin [174]. In our practice, we also had two HE cases positive for marker autoantibodies of autoimmune encephalitides (see below). The Japanese authors delineated a group of HE patients positive for aNAE, but negative for several other anti-cerebral autoantibodies, including those mentioned above. They did not reveal in them any tumors, thus interpreting this type of HE as non-paraneoplastic limbic autoimmune aNAE-encephalitis. The group was characteristic for acute onset of HE symptoms with predominance of consciousness and memory disturbances, psychotic symptoms and seizures [175].

In the very first publication coined the term of HE its authors already have stressed that it can be just a comorbid combination of a known highly spread disease – Hashimoto's autoimmune thyroiditis – with some still unknown and rare autoimmune brain disease [47]. Later A.M. Sawka et al. analyzing the materials of Mayo clinic for 46 years promoted the similar opinion on the essence of HE [176]. Now, having a long series of descriptions of new limbic autoimmune non-vascular encephalitides with various autoantibodies as their markers [128], we can appreciate the strength of these prophecies. It seems that part of HE cases, at least those with non-vascular involvement, really may belong to the family of autoimmune encephalitides.

## Global and our own experience of HE studies

According recent estimates, circa 400 cases of HE have been medically described up till now in more than 200 articles, those in English and Spanish languages were recently reviewed elsewhere [177].

There are also at least two books published about this disorder to date – one in USA with collection of HE patient's self-reports [178] and another one in Ukraine, with brief synopsis of the HE problem and description of single original and six literature cases of HE [179]. Our own contribution into HE studies consists of analysis of 17 cases. The aim was to identify possible relationships between their immune-endocrine parameters and neuropsychiatric symptoms. All patients suffered from Hashimoto's disease diagnosed according Japanese thyroidological association criteria (including increased levers of aTPO and anti-thyroglobulin autoantibodies) [24] and had also diagnosis of schizophrenia established in psychiatric clinic. The patients with autoimmune thyroiditis, but without diagnosed psycho-neurological diseases were enrolled as a group of comparison. We observed various psychiatric manifestations both in the group of patients with Hashimoto's thyroiditis in comorbidity with schizophrenia, and those having just autoimmune thyroiditis. In the group of patients with Hashimoto's thyroiditis and schizophrenia we observed such psychiatric symptoms as: Phobias (52%), generalized anxiety (18.5%), sleep disturbances (52%), irritability (6.5%), panic attacks (11%), and hallucinations (18.5%). Those patients having only Hashimoto's thyroiditis without comorbid psychiatric disorders displayed just phobias (53%) and sleep disturbances (52%), but not any other psychic manifestations. We revealed statistically reliable correlations between some laboratory and instrumental immuno-endocrine parameters and psychiatric manifestations. Thus, the risk of developing generalized anxiety as well as irritability increased in patients with the high level of autoantibodies to thyroglobulin, and also in those with higher prolactin and TSH blood levels as well as in lower levels of free thyroxine. The presence of nodules in the ultrasound image of thyroid gland correlated with greater risk of psychiatric symptoms. The risk of developing panic attacks was increased in patients having high level of autoantibodies to thyroglobulin, but also in those with higher concentrations of prolactin or TSH, and in cases with enlarged thyroid volume. The risk of developing hallucinations increased in patients with the high level of autoantibodies to thyroglobulin, but also in those with greater prolactin or TSH blood concentrations or lower free thyroxine levels. In addition, it was increased if nodules existed in the thyroid gland [180–182]. Hence, both anti-thyroid autoantibodies against thyroglobulin and hormonal changes related to hypothyroidism and its compensatory consequences could influence psychic status of patients. But, like in some earlier studies [183,184], level of aTPO in our research did not correlate with clinical manifestations of psychic disorders. In this group of HE patients we revealed two cases suspicious for autoimmune encephalitis: One case with schizophrenia-like symptoms positive for anti-NMDAR antibodies and another case of comorbidity of Hashimoto's thyroiditis and bipolar affective disorder positive for anti-GABAB antibodies [185,186]. We attempted to produce a mice model of HE using IgG isolated from HE patients with high level of aTPO by their intracisternal injections into mice brain, which article is now in press [187].

## Treatment and prognosis in HE

The treatment of HE is described in details elsewhere [55,177,188] and may include almost all approaches used in therapy of other autoimmunopathies. As it was mentioned above, the major part of cases, currently over 90% of them, are prone to glucocorticoid treatment with initial high dose (up to 1 g of methylprednisolone per day for adults or 30 mg/kg of body mass for children) administered for 3–7 days and subsequent supporting medium doses (1–2 mg/kg) tapered down slowly. In resistant cases of disease some authors recommended combinations of corticosteroids with other immunosuppressant, like azathioprine, methotrexate and rituximab. The last drug is used also for supporting treatment while tapering dosage of glucocorticoids down [177]. Thyroid hormones in HE serve not only as replacement therapy, but also for non-steroid immunomodulation and suppression of hyperprolactinemia, along with other prolactostatics [24,126]. Anti-hyperprolactinemic treatment is justified not only because of adjuvant-like action of prolactin on autoimmunity, but for improvement of reproductive potential. Reproductive failure *per se* can be additional psychopathogenic factor for HE patients (See above). One of the disputable questions is use of neuroleptics in HE as a kind of symptomatic therapy. They are in use [188], but their ability to stimulate prolactin secretion makes the approach to anti-psychotic therapy in HE different from that of classical primary psychoses. Anyway, alone such treatment can hardly fight psychotic symptoms of HE. The promising second line of treatment includes injections of human polyclonal intravenous donor's immunoglobulins (IVIG), which

were used successfully even as first line therapy in case of metabolic concerns for patient's obesity [71,177,188,189]. The Serbian authors reported the achievement of 7 year lasting remission after IVIG treatment in a HE patient poorly responded to glucocorticoids [190]. On the contrary, in Japan two cases of adverse effects from IVIG therapy (due to passive transfer of donor's anti-thyroid autoantibodies) were registered in autoimmune encephalitis patients [191]. Also procedure of plasmapheresis was successfully used in steroid non-responders and in case worsened after corticosteroids, presumably because of removal from blood certain (not necessarily anti-thyroid) autoantibodies or inflammatory mediators [192,193]. Sometimes plasmapheresis treatment may be long, up to 10 procedures, although as a rule 3 séances were enough for relief achievement [194]. Theoretically, cerebrospinal liquor adsorption should be effective in this illness, like in some other autoimmune neurological disorders, but it was not tested so far for treatment of HE patients.

The outcomes of HE vary, in majority of cases they are favorable with appropriate treatment, although after pausing of therapy in 12,5–40% of cases the relapses occur, as well as spontaneous reliefs were described [188,195]. Severe cases with early onset may result in serious psycho-neurological deficit, especially in early onset and/or late diagnosis, if they were non-treated on time [196].

## Conclusion

In spite of almost 200 years of scientists' efforts, still not all facets of thyroid/brain/immunity interactions are clear, and HE remains one of the enigmatic phenomena, both for Thyroidology and Psychiatry. The pathogenesis of HE may include direct action of various autoantibodies on target cells within CNS, like it occurs in autoimmune encephalitides, but also depends on indirect links, mediated *via* secondary cytokine production and/or metabolic effects of autoimmunity and changes in thyroid function. Recently it was shown that glucose metabolism in some areas or brain related to emotional and behavioral changes is altered both by ant-thyroglobulin autoantibodies and aTPO [197]. Nevertheless, psycho-neurological manifestations rightfully occupy their place in the mosaic of clinical symptoms of autoimmune thyroid disease and other autoimmune disorders commonly comorbid with thyroid ones [198,199]. An adequate animal model of HE may help to resolve its enigma [200].

## Declaration of Competing Interest

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**Practice points**

The practice points drawn from synopsis of HE studies include the following:

- HE should be suspected in any case of autoimmune thyroiditis with obvious neuropsychiatric symptoms (especially, cerebellar disorders, seizures and hallucinations), regardless of thyroid function status;
- Laboratory markers of HE (especially, elevated aTPO and aNAE in blood and cerebrospinal fluid) are useful for diagnosis although not always present, brain imaging may give additional diagnostic information, ECG and other liquor parameters are non-specific;
- Clinical picture maybe related not only to level of above mentioned autoantibodies, but also to presence of other autoreactive anticerebral immunoglobulins of minor specificities;
- Some cases of HE definitely belong to a sort of autoimmune limbic encephalitis, hence check for markers of non-paraneoplastic and paraneoplastic encephalitides is worth;
- Early complex treatment with glucocorticoids, thyroid hormones with IVIG and plasmapheresis as a second line is usually effective; neuroleptics should be used cautiously in view of vicious role of hyperprolactinemia.

**Research agenda**

The major pathophysiological considerations for next research agenda are following:

- Adjuvant-like factors are essential for etiology of HE, which may occur in co-morbidity with other autoimmunopathies;
- Hypoperfusion due to vasculitis, direct action of anti-thyroid and anti-cerebral autoantibodies on CNS and pathological/compensatory changes in hormone spectrum are intermingled in pathogenesis of HE;
- Translational medicine is in need for adequate animal model(s) of HE.

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