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Hashimoto's encephalopathy – an up-to-date overview

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Abstract

Introduction: Hashimoto's encephalopathy (HE) is a rare, potentially life-threatening disease with a wide spectrum of clinical manifestations from slight symptoms to mainly neurological and psychiatric syndromes, which significantly debilitate the quality of life and make the diagnostic process complicated, especially in patients with no previous history of thyroid

disorders. According to the recent data, it occurs in about 2.1 cases per 100 000 population with still increasing prevalence. Despite, over than fifty years have passed since the first case of HE was reported, its etiopathogenesis is not completely clarify and there is no universal diagnostic criteria.

Aim of the study: This article summarizes the current knowledge about pathophysiology, clinical manifestations, difficulties in differential diagnosis and therapeutic dilemmas in patients with HE.

Description of knowledge: HE is an autoimmune-mediated encephalopathy associated with Hashimoto's disease and elevated titers of anti-thyroid antibodies, mainly anti-thyroid peroxidase antibody. The diagnostic process is usually multi-step due to various diseases mimicking HE, such as Creutzfeldt-Jacob disease, brain tumors, epilepsy, Alzheimer's disease, stroke, other forms of autoimmune encephalitis, schizophrenia, spontaneous cerebrospinal fluid leak or infectious encephalitis. The range of diagnostic procedures includes physical and mental examination, laboratory tests, brain imaging, EEG as well as cerebrospinal fluid analysis. However, the first line strategy based on steroids is effective, there are some cases in the literature that reveal this management as not fully sufficient, because only partial improvement was achieved or the steroid-dependence was observed. Among other therapeutic methods, plasmapheresis may be used additionally.

Conclusions: HE requires interdisciplinary approach and it constitutes a great challenge for clinicians of various specialties, such as endocrinologists, neurologists, and psychiatrists. The prompt implementation of adequate therapy usually provides the full recovery of the patients without any early or late complications.

Keywords: Hashimoto's encephalopathy, autoimmune encephalopathy, anti-thyroid antibodies

Introduction

Hashimoto's encephalopathy (HE), also known as encephalopathy associated with autoimmune thyroid disease (EAATD), non-vasculitic autoimmune meningoencephalitis (NAIM) or steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is a rare disease with still increasing prevalence in recent years [1-3]. Its incidence

is accounted for about 2.1 cases per 100 000 people with the predilection for female gender and female-to-male ratio assessed for 4:1 to 5:1 according to different data [4-6]. The average age for HE occurrence ranges from 45 to 55 years [5]. However, the onset of the disease in children may start even from 14 months of age to adolescence with the peak at 14 years old [4,7-8].

It is characterized by a wide range of clinical manifestations from slight acute or subacute symptoms to mainly neurological and psychiatric syndromes, which significantly debilitate the quality of life and make the diagnostic process complicated, especially in patients with no previous history of thyroid disorders [9-10]. HE is usually associated with good prognosis, but when untreated it can be potentially life-threatening condition and may lead through coma up to death [4]. Although, the first-line therapeutic strategy based on steroids is effective, there are some cases in the literature that reveal this management as not fully sufficient, because only partial improvement was achieved or the steroid-dependence was observed [8,11-12]. That is why, HE requires interdisciplinary approach and it constitutes a great challenge for clinicians of various specialties, such as endocrinologists, neurologists, and psychiatrists.

Aim of the study

The aim of this review was to present both the most common and unusual clinical manifestations of HE. Moreover, we also discussed the diagnostic difficulties with the particular emphasis on diseases potentially mimicking HE as well as current and future therapeutic methods were presented.

Materials and methods

The available literature was subjectively selected due to its usefulness in showing clinical approach to diagnostic process and therapeutic strategies. We also presented series of described case reports to demonstrate the most common symptoms as well as unusual manifestations of this rare disease. Furthermore, data which reveals the differences in management of HE in children was shown as well. Eligible articles in English obtained from the EBSCO and the PubMed database from 2017 up to August 2019 have been analyzed using key words in various combinations: ‘Hashimoto’s encephalopathy’, ‘autoimmune encephalopathy’, ‘anti-thyroid antibodies’, ‘diagnosis’, ‘treatment methods’.

Description of knowledge

HE is an autoimmune-mediated encephalopathy associated with Hashimoto's disease and elevated titers of anti-thyroid antibodies, mainly anti-thyroid peroxidase antibody [13-14]. Although, the first report about HE was presented by Lord Brain et al. in 1966, its pathogenesis is still not completely understood and there is no universal diagnostic criteria [4,13,15]. Primarily, it has been hypothesized that thyrotropin-releasing hormone exerts toxic effects on the central nervous system as in a few cases the clinical condition of patients improved after the L-thyroxin substitution [16]. Nevertheless, most of recent studies suggested that autoimmune background plays a pivotal role in the development of Hashimoto's encephalopathy. This theory is strongly supported by HE co-existence with other autoimmune diseases like type 1 diabetes mellitus, myasthenia gravis, systemic lupus erythematosus, panniculitis, primary biliary cirrhosis, vitiligo in even 30% of individuals [4,17-18]. The researches revealed that autoimmune cerebral vasculitis proved by the presence of perivascular lymphocytic infiltration may be the main cause of HE, but pathological evidence on human brain's structure in HE are still scant [15-16,19]. Besides, some authors reported that there are two possible pathways leading to HE development. The first of them pointed to the role of anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg), and anti-TSH receptor (anti-TSHR) antibodies, which cause astrocytes damage and in this way change the brain functioning. On the other hand, the second one suggests the involvement of other antibodies, such as antibodies against the NH_2 terminal of α-enolase (anti-NAE antibodies) or IgG antibodies against dimethylargininase I or aldehyde reductase I, notwithstanding their exact mechanisms are not well known and further studies are necessary [4,14].

It is also worth to underline that nearly all cases of HE are associated with Hashimoto's disease, the most common autoimmune thyroid disorder. HE may develop both simultaneously with the diagnosis of sometimes undiagnosed previously Hashimoto' disease or even many years after the diagnosis. However, the hormonal status of thyroid gland differ among patients with HE. The recent evidence reported that euthyreosis was noted in approximately 18-45% of cases, 23-35% of individuals had subclinical hypothyroidism, 17-20% was diagnosed with hypothyroidism, and only 7% had hyperthyroidism [20].

As it was mentioned above, the diagnostic criteria are not well established, which may result in delayed diagnosis. According to analyzed series of case reports available in the literature, most authors suggested that the presence of neurological manifestations after excluding

another causes of encephalopathy, increased anti-thyroid antibodies in serum, and significant improvement after the administration of immunomodulatory treatment should be taken into consideration during the diagnostic process [Table 1].

Table 1. Diagnostic criteria for Hashimoto's encephalopathy [1,17].

Clinical presentations	Encephalopathy with cognitive impairment Encephalopathy with psychiatric manifestation Encephalopathy with partial or general seizures Encephalopathy with focal neurological deficits or alteration of consciousness
Laboratory tests	Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies Subclinical or mild overt thyroid disease (usually hypothyroidism) Absence of well-characterized neuronal antibodies in serum and CSF
Exclusion of neurological disease	Exclusion of neurological infection, toxic and metabolic disorder Brain MRI normal or with non-specific abnormalities
Response to treatment	Patient's neurological status return to baseline level after steroids therapy

Clinical manifestations of Hashimoto's disease

HE is characterized by a wide spectrum of clinical manifestations from weakness, fever, episodes of memory loss to severe neurological or mental disorders, which may lead to coma and death, if the improper therapy is applied [11,14,21]. We can distinguish two types of HE differing in the nature of presented symptoms. The vasculitic type (HE type 1) is characterized by the occurrence of stroke-like episodes accompanied by mild cognitive disorders in contrast to the diffuse one (HE type 2), wherein seizures, progressive dementia syndrome, disturbance of consciousness as well as psychotic symptoms are commonly observed [16,22]. HE can develop in an extremely insidious way and appear in an acute, subacute, chronic manner or may also take the remising-relapsing form.

Among all heterogenous symptoms of HE, neurological disorders are the most expressed. It is worth mentioning, that nearly two-thirds of patients (52-66%) experience episodes of seizures [23,24]. That symptoms are more commonly observed in children compared to adults [1]. Seizure disorders may initially occur as focal or generalized tonic-clonic convulsions [6,16], but there are some case reports in the analyzed literature, which described the HE presenting as status epilepticus (12% of patients) including epilepsies partialis continua (EPC) and non-convulsive status epilepticus (NCSE) [6,10]. Moreover, the

epileptic manifestations may have myoclonic or convulsive nature and what is more, the super refractory status epilepticus can appear [11,20,21]. The crucial issue is the remarkably low response to standard anticonvulsant therapy using lamotrigine, levetiracetam, sodium valproate, clobazam, phenobarbital, diazepam or phenytoin, which may provide lots of clinical problems [18,21]. Moreover, the presence of convulsive status epilepticus is considered to be a factor associated with the negative outcomes [6].

According to the analyzed available case reports, the complex of neurological symptoms of HE also contains the pyramidal tract signs, e.g. the presence of Babinski sign, gait ataxia, transient aphasia, dysarthria, the sleep impairments and/or headache [3,5,8,11,23]. Furthermore, *Emeksiz S. et al*. described the sensorimotor polyneuropathy in a 16-year-old girl as an extremely rare presentation of HE [25]. The variety of neurological manifestations requires from us to be aware of the possibility of HE mimicking by the signs of the brain tumor or Parkinsonism, such as monotoneus speech, muscle rigidity, mask-like face, hyperreflexia and the tumor-like lesions in imaging examination as well [19]. HE may also be misdiagnosed in case of the occurrence of focal neurological deficits accompanied with neck stiffness, vomiting, confusion and the hypertension or dyslipidemia in medical history, which all make a strong suspicion of acute stroke at a first glance [26].

The other worth-mentioning and common presentations of HE is the cognitive disturbances (36-100%), such as confusion, somnolence, and even coma [14,23,27,28]. It seems to be problematic to suspect HE in elderly people with the impairment in working memory, learning, processing speed, episodes of disorientation, and other neuropsychological disturbances, which strongly described dementia process [15,29,30].

What is more, psychiatric manifestations of HE constitute a significant proportion of all signs and should be taken into consideration. The acute psychosis (26.1%), depressive disorders (23.9%) as well as bipolar disease (15.2%) constitute the majority of all initially psychiatric diagnosis confused with HE and may occur alone or in combination with neurological symptoms [31]. The review of literature revealed, that this autoimmune encephalopathy can appear as hallucinations or other psychotic symptoms [6,18]. However, there are also some cases that described the depression as a mask of HE [31]. The patients usually complained about persistent and pervasive low mood, anhedonia, fatigability, and even the suicidal tendencies.

The overview of literature proved the possible presence of completely different symptoms from those characteristic for encephalopathy, such as urinary retention or panniculitis

associated with fever and polyarthralgia [5,17,23]. The most common symptoms and unusual manifestations of HE were presented on the examples of case reports and summarized in table 2 [Table 2].

Table 2. Clinical manifestations of Hashimoto's encephalopathy, diagnostic difficulties and therapeutic dilemmas – series of case reports between 2017 and 2019.

Study (Reference)	Sex	Age [Years]	Clinical manifestations	Mimicking disease	Previous history of thyroid disease	Hormonal status of thyroid	Anti-TPO [U/ml]	Anti-TG [U/ml]	Treatment	Complications
Tjong E et al., 2019 [2]	woman	60	intractable seizures since 34 years	epilepsy (episodic isolated delusional psychosis)	hypothyroidism	hypothyroidism (actually euthyreosis)	> 9540	< 3,5	methylprednisolone i.v. 1000 mg	recurrent delusions
Kaymakamzade B et al., 2019 [11]	man	76	myoclonus in all limbs and bilateral postural tremor, walking difficulty, motor weakness at the left lower extremity, Babinski sign (+),	delusions, aggressive behavior, vasculitis, paraneoplastic limbic encephalitis, Creutzfeldt-Jacob disease	no history	euthyreosis	40	431	methylprednisolone i.v. 1000 mg/day for 10 days IVIG 0.4 g/kg/day for 5 days azathioprine 100 mg/day	uncomplicated the patient died due to pneumonia
Ercoli T et al., 2019 [6]	woman	35	two focal seizures with impaired awareness, hallucinations, altered cognition, impaired consciousness	non convulsive status epilepticus	no data	no data	elevated	elevated	methylprednisolone 1000 mg i.v./ day for 5 days followed by prednisone p.o. IVIG 0.4 g/kg/day for 5 days	uncomplicated
Nagano M et al., 2019 [12]	woman	68	memory impaired, somnolence, consciousness disturbance	smoldering limbic encephalitis, severe, viral encephalitis, non-convulsive status	no data	euthyreosis	495	no data	methylprednisolone 1000 mg i.v./ day for 3 days followed by prednisolone	relapse of HE

				epilepticus					p.o.30 mg/day for 8 days, levetiracetam	
Navin K et al., 2018 [32]	woman	24	withdrawn and hallucinatory behavior, suicidal tendencies	severe depression with psychotic symptoms	no data	euthyreosis	> 1300	391.2	fluoxetine 20 mg, risperidone 2 mg, clonazepam 1,5 mg	uncomplicated
Cosso C et al., 2018 [17]	male	70	panniculitis, fever (up to 38 C), polyarthralgia	septal panniculitis	Hashimoto's thyroiditis	hypothyroidism (actually euthyreosis)	408	805.1	prednisolone 12.5 mg/day for 4 weeks	uncomplicated
Tomkins M et.al, 2018 [3]	women	59	recurrent falls and ataxia with speech impairment, poor concentration and drowsiness, bradycardia, hypotension, hypothermia	no data	Hashimoto's thyroiditis	hypothyroidism (actually euthyreosis)	38.5	no data	prednisolone 80 mg/day	uncomplicated
Tran M-Ha et al., 2018 [33]	woman	72	debilitating cerebellar gait ataxia, cognitive dysfunction	the HE diagnosis was previously made (cerebellar type)	Hashimoto's thyroiditis	no data	391.5	no data	corticosteroids, mycophenolate, immunoglobulin, long-term plasma exchange over an-2 year period	citrate toxicity, somnolence, lower limb spasm, recurrent infectious
Uwatoko H et al., 2018 [19]	woman	41	bipolar disorder, bradykinesia, coordination disorder, Parkinsonism	Parkinson disease, hyperreflexia, brain tumor	Hashimoto's thyroiditis	hypothyroidism (actually euthyreosis)	2008.93	249.48	brain biopsy, methylprednisolone 1000 mg i.v./day for 3 days followed by prednisolone 50	steroid psychosis

									mg/day	
Laycock K et.al, 2018 [9]	woman	28	chronic fatigue, lethargy, cognitive decline, poor concentration, generalized muscle aches and migraines	the HE diagnosis was previously made	Autoimmune hypothyroidism	hypothyroidism (actually euthyreosis)	1214	no data	IVIG	uncomplicated
Oz Tuncer G et al., 2018 [8]	man	14	right-side weakness, numbness, dysphagia, dysarthria, behavior disturbances, Babinski sign +	pseudobulbar palsy	no history	euthyreosis	998	no data	methylprednisolone i.v. for 5 days followed by prednisolone p.o. over 6 months	two recurrences after stopping steroid therapy
Sipilä JOT et al., 2018 [15]	man	89	episodes of disorientation, amnesia, moderate balance and cognition impairment, walking difficulty, tremor in the upper extremities	Alzheimer's disease	no history	euthyreosis	< 3	343	methylprednisolone i.v. 1000 mg/day for 3 days	uncomplicated
Kong F-X et al., 2018 [22]	woman	63	double vision, tired, paroxysmal dizziness, decline in memory	leukoaraiosis, cavernous hemangioma	no history	euthyreosis	1087	37.73	methylprednisolone i.v. 500 mg/day for 3 days, 250 mg/day for the next 3 days, 120 mg/day for 3 days followed by prednisone p.o. 60	uncomplicated

									mg/day	
Sabbah-Talasazan L et al., 2018 [29]	woman	76	cognitive deficits, impairment in memory, bilateral fine motor dexterity	dementia	no data	no data	no data	no data	steroids	uncomplicated
Ergul AB et al., 2018 [7]	man	14-month	myocarditis, spontaneous intramedullary hemorrhage (hemophilia A)	no data	no data	no data	53.9	11.8	fresh frozen plasma, IVIG 1g/kg for 2 days	poor response to therapy, autoimmunity lead to development of inhibitor to factor VIII
Sharma SR et al., 2018 [5]	woman (pregnant, 24. Hbd)	21	hiccuping, urinary retention, gait instability, weakness of limbs, dyspnea, nausea, vomiting, behavior disorders, unconsciuousness, Babinski sign +	psychosis	no history	hypothyroidism	686.9	no data	IVIG 0.4 g/kg/day for 5 days, methylprednisolone i.v. 500 mg/day for 5 days	fetal wastage
Gauthier AC et al., 2017 [28]	woman	55	subacute cognitive decline, ataxia	Creutzfeldt-Jacob disease	no history	subclinical hypothyroidism	966	no data	prednisone p.o. in 60 mg/day for one month with a planned tapper of 10 mg/month thereafter	uncomplicated
Rukmangadachar LA et al., 2017	woman	49	weakness, extremities clonic	epilepsy partialis continua, frontal lobe	chronic thyroiditis	euthyreosis	70	172.8	IVIG 2g/kg, prednisone 10-20	uncomplicated

[10]			twitching	lesion	(Hashimoto's, chronic lymphocytic thyroiditis?), thyroidectomy				mg/day, methyprednisolone i.v. 1000 mg/day for 3 days, prednisone p.o. 60 mg	
Gutch M et al., 2017 [16]	man	40	progresive alteration in sensorium, generalized tonic-clonic convulsions, hyperreflexia	the HE diagnosis was previously made	Hashimoto's thyroiditis	subclinical hypothyroidism	> 1000	no data	methyprednisolone i.v. 1000 mg/day for 5 days, prednisone p.o. 1 mg/kg/day	uncomplicated
Karthik MS et al., 2017 [20]	woman	19	mimic seizures during sleep, myoclonic jerks, acute confusion, psychomotor agitation, abnormal behavior	infective etiology, psychotic disorders	no history	euthyreosis	1261.4	no data	lorazepam 6 mg/day, olanzapine 5 mg/day followed by 15 mg/day methyprednisolone i.v. 750 mg/day for 5 days, prednisolone p.o. 45 mg/day	uncomplicated
Varrasi C et al., 2017 [18]	man	48	episodes of unilateral left-sided auditory hallucinations, dysgeusia, bizarre behavior	infective etiology, epilepsy	no history	euthyreosis	541	218	diazepam, i.v. phenytoin, carbamazepine, levetiracetam, lacosamide – lack of effect IVIG 0.4 mg/kg/day for 5 days, methyprednisolone	uncomplicated

									i.v. 1000 mg/day for 5 days	
Cooper BL et al., 2017 [23]	woman	26	urinary retention 2 months after postpartum, cognitive, memory impairment, hyperreflexia, Babinski, Hoffman's reflexes ++, clonus	neoplasm, autoimmune vasculitis, disturbances in the upper motor neuron	no history	euthyreosis	123	normal	methyprednisolone i.v. 1000 mg/day for 3 days	uncomplicated
Simmons SC et al., 2017 [34]	woman	55	gait ataxia, memory loss, mood change	stroke, brain tumor, demyelinization disease	no history	no data	> 1000	no data	mycophenolate mofetil, therapeutic plasma exchange	mild citrate toxicity
	woman	49	insomnia, altered state of consciousness, mental symptoms	psychiatric disturbances	no history	no data	> 1000	no data	steroids, IVIG, therapeutic plasma exchange	transient hypotension, headache
Alazzeh A et al., 2017 [26]	man	49	neck stiffness, vomititng, confusion, tremor, strange behavior	viral/bacterial meningitis, encephalitis, metabolic encephalopathy, acute ischemic/haemorrhagic stroke, multiple sclerosis, cerebral vasculitis, epilepsy, brain abscess, chronic inflammatory demyelinating	no history	euthyreosis	124	98	vancomycin, ceftriaxone, acyclovir methyprednisolone i.v. 1000 mg/day for 3 days, azathioprine 100 mg/day, prednisone p.o. 20 mg	mild degree ataxia

				polineuropathy, epidural abscess, Guillain-Barre syndrome, Lambert Eaton syndrome						
Al-Busaidi M et al., 2017 [21]	woman (pregnant 8. hbd)	38	fever, abdominal pain, depressed level of consciousness, generalized tonic-clonic seizures	refractory status epilepticus	no history	no data	222	no data	midazolam, propofol, ketamine, thiopentone i.v., phenytoin, acyclovir, lamotrigine, levetiracetam, sodium valproate, clobazam, phenobarbital, lacosamide methyprednisolone i.v. 1000 mg/day for 5 days, IVIG i.v. for 5 days, plasma exchange therapy	lack of seizure control, pseudomonal sepsis with multiple organ failure, patient died on day 18 after admisssion
Hirose D et al., 2017 [14]	man	78	sudden attack of consciousness disturbance, coma, akinetic mutism, severe muscular rigidity	Creutzfeldt-Jacob disease	Hashimoto's thyroiditis	euthyreosis	179	no data	methyprednisolone i.v. 1000 mg/day for 3 days	died of respiratory insufficiency

Endres D et al., 2017 [30]	woman	59	rapid onset dementia, apathy, verbal depletion, severe memory deficits, micturition disorder, catatonic features	behavioral variant of frontotemporal dementia	Hashimoto's thyroiditis	subclinical hypothyroidism	84	832	antidepressants, neuroleptics, anxiolytics methyprednisolone 5 x 500 mg/day for 5 days, plasma exchange therapy	unsucessful therapy with steroids, reduced oral fluency
Chen K-A et al., 2017 [13]	woman	10	progressive ataxia, dysarthria, altered behaviour	the HE diagnosis was previously made	Hashimoto's thyroiditis	euthyreosis	61	2719	methyprednisolone i.v. 1000 mg/day for 5 days, prednisolone p.o. for nine months	uncomplicated

Diseases mimicking Hashimoto's encephalopathy – difficulties in the differential diagnosis

The diagnostic process is usually highly complicated due to the non-specific symptoms of HE mimicking other diseases as in the above-mentioned cases shown in table 2 [Table 2]. In case of HE there are three principal steps allowing for making the diagnosis: diversity of clinical manifestations, elevated level of anti-thyroid antibodies as well as good response for steroids [1]. Whereas the diagnosis of severe forms is not usually a problem, milder forms of HE can be misdiagnosed as general encephalitis or psychosomatic disorders.

The range of diagnostic procedures involves physical and mental examination with particular emphasis on neurological examination and tests assessing cognitive functions, laboratory tests, brain imaging, electroencephalography (EEG) as well as cerebrospinal fluid analysis. As the literature overview revealed, the first step in the diagnostic process requires the exclusion of most common causes of various range of neuropsychiatric symptoms presented by the patient, such as stroke, epilepsy, infectious encephalitis, multiple myeloma, brain tumors, Alzheimer's disease, dementia, Parkinson's disease, other forms of autoimmune encephalitis, including forms of limbic encephalitis like anti-NMDA receptor encephalitis, schizophrenia, spontaneous cerebrospinal fluid leak or Creutzfeldt-Jacob disease.

Moreover, CSF should also be analyzed to assess the cytology, protein and glucose levels as well as to exclude the presence of bacterial culture, viral antibodies like anti-HSV, anti-CMV, West Nile virus antibodies, ANA, anti-double-stranded DNA, paraneoplastic autoantibody panel as anti-Hu or anti-Ri, 14-3-3 protein, t-tau protein, and oligoclonal bands. [6,14-15,28]. Although, anti-thyroid antibodies may also be found in CSF, but their detection in CSF is not characteristic for HE and they can appear in other central nervous system pathologies.

EEG is a useful tool in the differential diagnosis of HE, but has limitations. In most cases, the abnormal EEG results were observed, but they appeared as rather non-specific findings. Taking into consideration the fact that, seizure disorders predominantly occurred as a manifestation of HE, determination their cause was complicated. Besides this, EEG seems to be essential in reflecting changes in brain during therapeutic process as well as follow-up.

The neuroimaging including computed tomography (CT) or magnetic resonance (MR) imaging were always performed. The results of these examinations range from normal to non-specific (50%) or sometimes mimic (49-50%) an ischemic stroke (ischemic lesions), brain tumors and degenerative diseases (white matter changes) [1,4,19,26].

From a clinical standpoint, it is quite important to differentiate between HE and diseases potentially mimicking this condition from other autoimmune encephalitis. That is why, the assessment of thyroid function with the determination of thyroxine, triiodothyronine should be performed. Nevertheless, in most case there was no significant deviations or patients were in euthyreosis due to pharmacological supplementary. The crucial issue for making the diagnosis is measurements of the anti-thyroid antibodies concentration: anti-Tg and especially anti-TPO. To date, there is no clear consensus about the cutoff value of anti-TPO antibodies. However, some authors suggest that it should be ≥ 200 μUI/mL in at least one of antibodies would strongly eject a suspicion of HE [4]. What is important, anti-bodies do not correlate with the severity of the disease, but they may be used as a predictor of response for the treatment [30].

What is more, high attention is focused on newly discovered auto-antibodies against the NH_2 terminal of α-enolase (NAE) as a serum biomarker of HE. According to the cross-sectional studies, they were present in approximately 50% of the patients diagnosed with HE. Moreover, they were also proposed as candidates for hallmarks of HE [14].

Dilemmas in the treatment of Hashimoto's encephalopathy – current status and future perspectives

Numerous studies demonstrated that there are two possible pathways in management of HE. The first method is usually based on symptomatic treatment, but even almost failed, in contrast to the second one, which is causal treatment of HE.

According to the recent data, most of patients after proper therapy achieve the complete recover, but the relapse may occur in approximately 12.5-40% of cases in follow-ups to two years [4]. While late neurological complications were not reported in adults so far, disturbances in central nervous system in children were estimated at more than 20% of them after a four-year observation [4].

HE is usually successfully treated with corticosteroids, that is methylprednisolone administered intravenously in the dose of 1 g in adults and 20-30 mg/day in children per 3-7 days, followed by prednisone/prednisolone applying orally in the dose of 50-150 mg a day or 1-2 mg/kg of body weight a day with gradual dose reduction as we shown in case reports summarized in table 2. What is more, it is believed that maintenance corticosteroid therapy should be continued for even 1-2 years, which reduced the risk of HE recurrence. However, in about 12.5% of HE cases, steroid-resistance occur and it requires additional treatment

methods [4,14,30]. So far, there is no universal therapeutic scheme in such cases of patients and intravenous immunoglobulin (IVIG) at a dose of 0.4 mg/kg/day for 5 days or immunotherapy with cyclophosphamide, azathioprine, mycophenolate mofetil should be applied. The same management is recommended in case of contraindications for above-mentioned regimens implementation.

However, if the standard therapy is ineffective or the response seems to be poor after at least 4-6 weeks of a sufficient dose of steroids, plasma exchange therapy (TPE) rises high hope in management with patients suffering from HE [30,33-35]. TPE seems to be a safe method of treatment, because only mild side effects, such as mild citrate toxicity, transient hypotension, headache, hypocalcemia were usually observed [34]. The current guidelines recommended that the number of performed TPE should be five once every other day (ranging from 3 to 9 sessions). What is more, nearly 90% of patients with HE showed a significant improvement and the symptoms relieved [35].

Besides, except from causal treatment, drugs relieving symptoms and preventing the early or late complications should be also applied. Among them, mannitol to reduce cerebral edema and antiepileptic drugs in case of seizures as well as anti-depressants in some cases are commonly used.

Conclusions

To conclude, Hashimoto's encephalopathy is a rare, but potentially life-threatening condition. It requires interdisciplinary approach and constitutes a great challenge for clinicians of various specialties, such as endocrinologists, neurologists, and psychiatrists. The timely implementation of adequate therapy usually provides the full recovery of the patients without any early or late complications.

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