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Published in:
European Journal of Paediatric Neurology

DOI:
10.1016/j.ejpn.2021.04.006

Publication date:
2021

European Journal of Paediatric Neurology 32 (2021) 122–127

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

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ARTICLE INFO

Article history:
Received 14 August 2020
Received in revised form
21 April 2021
Accepted 25 April 2021

Keywords:
Hashimoto's encephalopathy
Systemic corticosteroids
Anti-thyroidperoxidase
Coma
Epileptic state

ABSTRACT

Background: Hashimoto's encephalopathy, also known as steroid responsive encephalopathy, is associated with thyroid antibodies (SREAT) and is a rare but serious form of encephalopathy. In this paper, we describe the signs, symptoms, outcome, and treatments as noted in the case reports reviewed.
Methods: We searched PubMed, Embase, and the Cochrane library for articles in which cases of Hashimoto's encephalopathy were described. The case description had to include the diagnosis, age, sex, presenting symptoms, and diagnostic tests.
Results: We retrieved 360 articles and 65 fulfilled the inclusion criteria. These articles gave reports of 100 cases, with a mean age of 10.9 (range 2.8–19), 78 of whom were female. Epilepsy (79) – including epileptic state [24] – behavioural problems [36], hallucinations [21], headache [21], and decline in school performance [19] were most often reported. Antithyroid peroxidase (aTPO) was reported elevated in all patients. Most children [70] recovered fully, however 16 had late sequelae, mostly epilepsy. Therapies used include steroids, intravenous gammaglobulines, and cytostatics.
Conclusions: Epilepsy, behavioural problems, decline in school performance, and hallucinations are frequent symptoms of Hashimoto's encephalopathy. Steroids are the basis of treatment, although other immunomodulatory drugs seem to be successful. About one in ten children will experience late sequelae. In any child with unexplained neurological, psychiatric, or psychological dysfunction, serum *anti*-thyroidperoxidase (aTPO) should be determined.

1. Introduction

Hashimoto's encephalopathy, also known as steroid responsive encephalopathy associated with thyroid antibodies (SREAT) is rare in children and adolescents [1,3]. The estimated prevalence in adults is 2.1/100.000 [2], the prevalence in children is unknown. The condition has a wide variety of severe neurologic symptoms and its pathogenesis is still unknown. In all patients an increased level of serum *anti*-thyroidperoxidase (aTPO) [4], independent of thyroid status, is found. Despite an elevated level of aTPO in all patients, these antibodies do not play any role in the pathogenesis. In most patients, treatment is effective and leads to disappearance of symptoms [5]. Therefore, early recognition is important and possible. In 2008, we reviewed the presenting signs and symptoms in 25 cases reported [6].

We wanted to determine whether the reported spectrum of signs and symptoms has broadened since 2007, which signs and symptoms have been described most frequently, and whether new presenting features have been described. Therefore, we studied clinical reports of paediatric patients with Hashimoto's encephalopathy.

2. Methods

We searched the literature for as many paediatric cases of Hashimoto's encephalopathy as possible from 2008/01/01 to 2019/10/01.

To find all paediatric cases of Hashimoto's encephalopathy, we searched for cases and clinical reports in PubMed, Cochrane Library and Embase using the following terms:

("Hashimoto Disease"[Mesh] OR "Hashimoto's encephalitis"

Abbreviations: SREAT, teroid responsive encephalopathy associated with thyroid antibodies; aTPO, antithyroid peroxidase; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; EEG, electroencephalography; ADHD, attention deficit and hyperactivity disorder.

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https://doi.org/10.1016/j.ejpn.2021.04.006
1090-3798/

[Supplementary Concept] OR Hashimoto encephalopathy [tiab] OR Hashimoto's encephalopathy [tiab] OR Hashimoto's encephalitis [tiab] OR Hashimoto encephalitis [tiab] OR Hashimoto Disease* [tiab] OR Hashimoto's Disease [tiab] OR Hashimoto Thyroiditis [tiab] OR Hashimoto's Thyroiditis [tiab]) AND (child*[tw] OR schoolchild*[tw] OR infan*[tw] OR adolescen*[tw] OR paediatri* [tw] OR paediatr*[tw] OR neonat*[tw] OR boy [tw] OR boys [tw] OR boyhood [tw] OR girl [tw] OR girls [tw] OR girlhood [tw] OR youth [tw] OR youths [tw] OR baby [tw] OR babies [tw] OR toddler*[tw] OR teen [tw] OR teens [tw] OR teenager*[tw] OR newborn*[tw] OR postneonat*[tw] OR postnat*[tw] OR puberty [tw] OR preschool* [tw] OR suckling*[tw] AND ("2008/01/01" [Date - Entrez]: "3000" [Date - Entrez])

We also searched in the references of the articles found. For reviewing individual reports, we used the PRISMA statement. We included articles with one or more cases reported. The articles had to give details of cases, including established diagnosis of Hashimoto's encephalitis, age, sex, clinical symptoms, and diagnostic procedures. Articles in which only specific elements, such as thyroid status, of groups of children were studied, were excluded.

From the articles, we gathered information on sex, age, presenting symptoms, and signs, as well as the outcomes of further laboratory, imaging, and neurophysiologic studies. Furthermore, we reviewed the treatment given and the outcome as reported.

3. Results

We found 360 articles and could include 65 [7–20, 21-40, 41-60,61–72]. These articles reported on 100 children, their median age was 10.9 years old and the age ranged from 2.8 to 19 years. Most of the children were female (78) (female: male ratio = 4:1). Epilepsy was the most reported symptom and was described in 79 out of 100 cases. Epileptic features varied from generalized tonic-clonic convulsions with duration of less than 5 min to epileptic state with duration of several hours. Other frequently reported neurologic symptoms were coma (18), dysarthria (13), hemiparesis (9), and ataxia (11). Hallucinations (21), confusion (17), anxiety (4), and depression (3) were reported psychiatric symptoms. The reported psychological and cognitive symptoms include behavioural problems (36), decline in school and cognitive performance (19), and agitation or aggression (18) (Table 1). Besides convulsions, alterations in psychological and cognitive functioning were the most often reported early symptom. Twenty children had only neurological symptoms, mostly epilepsy. Sixty-three patients had a combination of neurological, psychiatric, and psychological symptoms. Table 2 shows the clinical symptoms of these 100 reported cases combined with the 25 of our earlier study (see Table 3).

Table 1
Clinical symptoms, described in 100 patients younger than 19 years old in whom a diagnosis of Hashimoto's encephalopathy was established.

Clinical symptoms	New search N = 100
Generalized tonic-clonic convulsions	55
Epileptic state	24
Behavioural problems	36
Hallucinations	21
Confusion	17
Headache	21
Coma/unconsciousness/stupor	18
Aggression/agitation	18
Hemiparesis	9
Tremor	8
Ataxia	11
Encephalopathy unspecified	8
Diplopia	6
Sleepiness	5
Sleeping problems/insomnia	8
Disorientation	5
Myoclonus	4
Anxiety	4
Decline in school performance	19
ADHD ([a])	6
Dysarthria	13
Hyperreflexia	3
Skin rash	2
Urinary incontinence	2
Amnesia	6
Depression	3
Muscle weakness	8

[a] ADHD = attention deficit hyperactivity disorder.

3.1. Laboratory results

Antithyroid peroxidase (aTPO) was reported elevated in all 100 patients. The values of serum levels of 33 patients were reported and ranged from 67 to 7000 U/l (mean 1228 U/l; standard deviation 1429 U/l). In the child with the lowest value of 67 U/l, the cut-off point in that hospital was reported as 30 U/l. In 31 patients, antithyroglobulin antibodies were measured, with 28 patients (90%) having elevated values.

About two-third of the patients (62) were euthyroid, 35 were hypothyroid, and three were hyperthyroid (Table 2a). Numerous other laboratory studies, including assessment of infection parameters, organ function, and serology for other autoantibodies or antibodies against viruses, were performed.

In 22 of the 50 children (44%) in whom a lumbar puncture was performed, the protein concentration in the cerebrospinal fluid (CSF) was elevated. Five out of the ten patients (50%) in whom aTPO in the CSF was tested, a positive result was described (Table 2).

3.2. Imaging studies

The results of Magnetic Resonance Imaging (MRI)-scanning were available for 72 patients, and 48 (67%) of these were reported as normal. Nonspecific abnormalities reported were asymmetric multifocal hyperintensity signals, global atrophy, cortical oedema, and calcifications (Table 2c).

3.3. Electroencephalography (EEG)

An EEG was performed on 96 of the patients and was normal in only 20 of them (21%). In 38 patients (40%), background slowing was reported found and in 20 (21%) epileptic discharges were described (Table 2c). A pattern, as seen in encephalopathy, was reported for nine patients. In the remaining patients, abnormalities were not specified.

3.4. Treatment

Most children were treated with systemic corticosteroids (79). Typical corticosteroid regimens included 500–1000 mg methylprednisolone for three or five days followed by oral prednisolone 1–2 mg/kg body weight/day. Then, prednisolone was tapered in two or three weeks. In other cases, oral prednisolone was the first prescribed drug. Intravenous gamma globulins were given in 17, in most together with the corticosteroids. Other immunomodulatory treatments used, after steroid failure, were plasmapheresis [7] and cytostatic drugs [5] (Table 2d). Other medications given included antiepileptic drugs (18) and thyroid medication [33].

3.5. Outcome

Most children (70) made a complete recovery without any clinical disabilities. None of the children died. Fifteen children

Table 2
Laboratory and imaging studies in children with Hashimoto's encephalopathy.

Thyroid status of children with Hashimoto's encephalopathy	
Thyroid status in serum	N = 100
Hypothyroid	35
Euthyroid	62
Hyperthyroid	3
Antimicrosomal antibodies	100
Antithyroglobulin antibodies **(N = 31)**	28
Cerebrospinal fluid in children with Hashimoto's encephalopathy	
Cerebrospinal fluid analysis	N = 50 (%)
Normal	23 (46)
Elevated protein concentration	22 (44)
Positive *anti*-thyroidperoxidase **(N = 10)**	5 (10)
Elevated monocytes	2 (4)
Imaging studies and results of electroencephalography performed on children with Hashimoto's encephalopathy	
MRI T2/FLAIR	N = 72 (%)
Normal	48 (67)
Asymmetric multifocal hyperintensity signal in different foci	7 (10)
White matter lesions	5 (7)
Hyperintensity signal hippocampus	5 (7)
Global atrophy	3 (4)
Other (i.e. calcifications, cortical oedema, subacute infarctions, meningeal enhancement)	4 (6)
EEG	**N = 96 (%)**
Normal	20 (21)
Background slowing	38 (40)
Epileptic discharges	20 (21)
Encephalopathy (focal or generalized)	9 (13)
Abnormal electroencephalographic findings unspecified	9 (13)
Treatments administered to children with Hashimoto's encephalopathy	
Treatment	N = 100
Steroid therapy	79
Antiepileptic drugs	18
Thyroid medication	33
Plasmapheresis	7
Intravenous immunoglobulin	14
Cytostatics	5
Antipsychotics	5
Antidepression drugs	4
Acetylsalicylic acid	2
No treatment described	7

experienced a relapse. Sixteen children suffered impairment of neurological functions, mostly convulsions, at least three months after recovery. In five children the impairment of cognitive functions remained.

4. Discussion

In this study, we expand the clinical understanding of signs and symptoms in children with Hashimoto's encephalopathy. One hundred new cases have been reported since our earlier publication. The most frequent neurological features of Hashimoto's encephalopathy were convulsions, epileptic state, hemiparesis, and coma. Diplopia, dysarthria, and unspecified encephalopathy were reported as other relatively frequent neurological symptoms. The most reported psychiatric symptoms were hallucinations and confusion. Repeatedly reported psychological symptoms include behavioural problems and decline in school and cognitive performance. Other symptoms reported were agitation or aggression and behavioural symptoms that mimic attention deficit and hyperactivity disorder (ADHD). Sleeping problems, muscle weakness, and myoclonus were reported also. Most children displayed more than one sign or symptom. Two-thirds of the patients had a combination of neurological, psychiatric, and psychological symptoms. There was a wide variety in presenting symptoms. In some children neurological symptoms such as coma or epileptic state were the first symptoms. In other patients psychological symptoms such as mood alterations or cognitive disfunction came first. The youngest child reported was 2.8 years old.

4.1. Neurology

Compared with our earlier study, Hashimoto's encephalopathy has been recognized more often in an epileptic state. Altered mental state and coma have been described relatively often also. The variety of other neurological signs signals an involvement of different parts of the brain in Hashimoto's encephalopathy. Surprisingly, hyperreflexia, myoclonus, muscle weakness, and urinary incontinence were described also. We could not find any explanation for these symptoms.

4.2. Psychiatry and psychology

As in our earlier report, hallucinations were observed relatively frequently (21/100). Obviously, hallucinating is an important symptom of Hashimoto's encephalopathy. A wide variety of psychological symptoms, such as behavioural problems, decline in school performance, aggression, and sleeping problems have been observed in the patients. Some of these symptoms were reported to

Table 3
Clinical symptoms of 125 patients younger than 19 years old in whom the diagnosis Hashimoto's encephalopathy was established. In this table, the results of the present study and the earlier study are aggregated.

Clinical symptoms	New search n = 100	Earlier study n = 25	Aggregated n = 125 (%)
Generalized tonic-clonic convulsions	55	20	75 (60)
Epileptic state	24	1	25 (20)
Behavioural problems, altered mental state	36	5	41 (33)
Hallucinations	21	8	29 (23)
Confusion	17	13	30 (24)
Headache	21	10	31 (25)
Coma/unconsciousness/stupor	18	15	33 (26)
Aggression/agitation	18	10	28 (22)
Hemiparesis	9	7	16 (13)
Tremor	8	7	15 (12)
Ataxia	11	8	19 (15)
Encephalopathy unspecified	8		8 (6)
Diplopia	6	1	7 (6)
Sleepiness	5	9	14 (11)
Sleeping problems/insomnia	8		8 (6)
Disorientation	5	7	12 (10)
Myoclonus	4	6	10 (8)
Anxiety	4		4 (3)
Decline in school performance	19	7	26 (21)
ADHD ([a])	6	7	13 (10)
Dysarthria	13	9	22 (18)
Hyperreflexia	3	4	7 (6)
Skin rash	2		2 (2)
Vomiting		6	6 (5)
Urinary incontinence	2		2 (2)
Amnesia	6	3	9 (7)
Depression	3	3	6 (5)
Muscle weakness	8		8 (6)

[a] ADHD = attention deficit hyperactivity disorder.

be present before the neurological symptoms began. However, it is difficult to determine whether these are early symptoms. However, when there is a decline in a child's cognitive functioning and school performance, which are otherwise not explained, Hashimoto's encephalopathy must be considered.

4.3. Age

Compared with our earlier report, the median age of the children described is lower, with the youngest patient being less than three years old. This difference could be a reflection of simply including younger children in the differential diagnosis.

4.4. Other investigations

Most children underwent a variety of laboratory and imaging studies. This process is inevitable since many diseases, such as tumours and infections, can cause such a variety of symptoms. However, we suggest ordering thyroid antibodies such as aTPO in serum in all children with an epileptic state, in a coma, or with signs of encephalopathy. Although an elevated aTPO can be found in otherwise healthy children, the aTPO level in patients with Hashimoto's encephalopathy described ranged from twice till hundredfold. Moreover, in otherwise healthy children with no risk factors who develop rare neurological, psychiatric, or psychological problems for which laboratory testing is considered, determination of aTPO should be included.

Noticeably, in almost two third of all reported cases a euthyroid status was reported. This is in line with the outcome of an earlier study in children and adolescents with Hashimoto's encephalopathy where normal thyroid function was found in 11 of the 17 patients studied [74]. In adults, subclinical of mild overt thyroid disease is considered a diagnostic criterion [75].

4.5. Treatment & outcome

Most of the children recovered, sometimes after more than one course of high doses of systemic corticosteroids. Some children were reported to be successfully treated with plasmapheresis, cytostatics, or monoclonal antibodies. These immunomodulatory treatments are often used in children and adults with auto-immune disorders.

4.6. Comparison

Compared with our earlier study, the number of children presenting with epilepsy, including epileptic state, is high. Furthermore, many children were reported as displaying behavioural problems, such as aggression and agitation. A relatively high number of cases reported decline of school performance.

Laurent et al. summarized the reports of 251 adult cases [73]. Among adults, women seem to be more susceptible to Hashimoto's encephalopathy, since 75% of the patients described were female. Of course, the differential diagnoses in adulthood differ from those in children. Half the adult patients described had epilepsy, which is less than in our paediatric population. Almost half the adults displayed confusion; whereas, in our children's group, the percentage of confusion was 20%. However, the outcome among adults seems to be comparable to that among children. In children, 70% had a complete recovery, and, in adults, 91% had a complete or partial remission. However, in the adult group, half the patients were still on steroids. In the adult series, 6% of the patients died; whereas, in the children group, all survived.

4.7. Limitations

Inevitably, a review based on case reports will never provide a complete and exact clinical understanding. However, since

Hashimoto's encephalopathy is a rare disease, this method is the only way to learn about signs and symptoms. We acknowledge that not all patients who are diagnosed with Hashimoto's encephalopathy are reported in the literature. Therefore, we cannot be certain about the exact frequencies of the signs and symptoms reported. However, this study is not meant to provide exact figures; its aim is to help clinicians to recognize the disease. Another limitation is that we cannot be sure that some of the cases described actually had another diagnosis. However, we think that the author who publishes a case will be convinced of the diagnosis.

5. Conclusions

In conclusion, when the signs and symptoms of all 125 patients of this and our earlier study are aggregated, we suggest including the diagnosis of Hashimoto's encephalopathy in children with an epileptic state, refractory epilepsy, coma, and with rare neurological or psychiatric signs and symptoms. The disease can be found even in young children. We advise including determination of serum aTPO in children with these symptoms, irrespective of thyroid disease. A strongly elevated level of aTPO, typically more than tenfold the upper reference level, supports the diagnosis. However, careful consideration is required to rule out other aetiologies, specifically in children with slightly elevated antibody titres. High dose corticosteroids are the first choice of medical treatment. In some cases, immunomodulatory therapy seemed to be helpful. Most, but not all, patients recover completely.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

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