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CASE REPORT

Down syndrome and Hashimoto's encephalitis

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KEYWORDS
Hashimoto's encephalitis;
Down syndrome;
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Abstract
This review and discussion of current literature is based on the case of a teenager with Down syndrome (DS) who presents symptoms compatible with Hashimoto's encephalitis (HE).
Clinical case. A sixteen-year-old male with DS had a subacute onset of neuropsychiatric symptoms. Hashimoto's thyroiditis (HT) was confirmed and steroid treatment initiated, with positive results, so the diagnosis of HE was made.
Discussion. HT is a particularly common disease among patients that usually have autoimmune disorders, such as persons with DS. HE is a treatable condition that is poorly recognized in children and has been reported only twice with DS.

PALABRAS CLAVE
Encefalitis de Hashimoto;
Síndrome de Down;
Corticoides

Síndrome de Down y encefalitis de Hashimoto

Resumen
Discusión y revisión de la literatura a partir del caso de un adolescente con síndrome de Down (SD) y sintomatología compatible con encefalitis de Hashimoto (EH).
Caso clínico. Varón de 16 años con SD que de forma subaguda inicia síntomas neuropsiquiátricos. Tras confirmarse una tiroiditis de Hashimoto (TH) y tratado favorablemente con corticoides, se llega al diagnóstico de EH.
Discusión. La TH es frecuente sobre todo en pacientes con tendencia a padecer enfermedades autoinmunes como en el SD. La EH se trata de una patología escasamente descrita en la edad pediátrica, tratable, que sólo ha sido comunicada en 2 pacientes con SD.

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Introduction

Hashimoto's thyroiditis is a well-defined autoimmune entity produced by antibodies acting against the thyroid gland, triggering glandular dysfunction which is evidenced as hypothyroidism, hyperthyroidism or thyrotoxicosis. Predominantly affecting females, it is the main cause of thyroiditis among schoolchildren and adults, and has an annual incidence of 1.2%in the school-age population.

Both congenital and acquired hypothyroidism are more common in people with Down syndrome (DS) than in the general population, with an estimated prevalence of between 9% and 35% Hashimoto's thyroiditis is the main cause of acquired hypothyroidism in this population[1].

The part played by thyroid disease in central nervous system disorders was first suggested in 1880 when psychiatric and neurological findings were made in patients with hypothyroidism and myxedema. In 1912, Hakaru Hashimoto first described the thyroiditis that takes his name[2]. The term Hashimoto's encephalopathy was coined by Lord Brain in 1966 when he discovered a patient with neurological symptoms during fluctuations in thyroid activity[3].

This entity has had many names, the classic one being Hashimoto's encephalopathy, but a more descriptive one is "steroid-responsive encephalopathy associated with autoimmune thyroiditis" and/or "non-vasculitic autoimmune meningocephalitis". Although first described in adults, in recent years the various reviews of paediatric cases have been added to the literature. These are mainly with adolescent children, but there are also a few cases of subjects under 10, the youngest being 2 years and 10 months old[4,5]. Few cases have been published which refer to its association with Down syndrome, there being only 2 cases in adult women[6].

The symptoms of Hashimoto's thyroiditis include the appearance of neurological and psychiatric disorders such as sleep disturbances, hallucinations, psychosis/paranoia, migraine, aphasia, tremor, ataxia, convulsions and myoclonus. These symptoms can be acute or subacute and have a persistent or fluctuating course. In an attempt to categorize its diverse clinical characteristics Hashimoto's encephalopathy has been divided into two sub-types: a vasculitic presentation with stroke-like events and another diffuse progressive form with a predominance of dementia and convulsions[7-9].

Here, we describe a patient with Down syndrome and progressive neuropsychiatric symptoms in the context of Hashimoto's thyroiditis who shows a partial response to steroid treatment.

Clinical case

The subject was a severely mental retarded 16 year old male with Down syndrome, and with a psycho-behavioural profile compatible with autism and with no language development. The symptoms, with an evolution of 18 months, were characterized by: crises of psychomotor agitation, behavioural disorders consisting of throwing nearby objects, and auto—and heteroaggressive behaviour towards his carers, requiring physical restraint to control him. These episodes last between 3 and 8 h, 3 or 4 times per week, with alternating periods of lethargy during which he will not respond to simple orders.

Despite the patient's symptoms at the time of the study, prior to this he is known to have had a stable lifestyle. He attended a special school normally, and at home he had acquired an acceptable functional level in everyday routines, which he started to lose progressively.

Due to the persistence of the behavioural disturbances, the patient was treated as an outpatient with chlorpromazine, olanzapine, resperidone and valproic acid, with no improvement seen. The clinical symptoms got worse when they included sleep disturbances and oppositional behaviour (he refused to walk and stayed on the floor for hours).

Autoimmune subclinical hypothyroidism, with evidence of antithyroid antibodies, stands out on his medical record. This was diagnosed when he was 9 years old and treated with 25 mg/day of thyroxin (Table 1).

Due to worsening symptoms, he was admitted for study to the Sant Joan de Déu hospital in Barcelona. At the time of admission the patient was conscious and haemodynamically stable. The physical examination was limited by the patient's lack of cooperation and aggressive behaviour. The initial assessment revealed bradykinesia and no language skills. He only communicated with gestures and screams. There were no signs of goitre or the pairs of cranial nerves being affected. Muscular strength was normal and his four limbs were symmetrical. There was evidence of slight axial hypotonia and hyporeflexia. There were no signs of spasticity; autonomous walking was stable and there were no cerebral signs.

The complimentary studies were normal (metabolic study, cranial MR scan and EEG), thus ruling out other

Table 1 Evolution of thyroid function

Date	Jan 2009	March 2007	February 2006	September 2005	July 2004	November 2003	July 2002	November 2000	Jan 2000
TSH (nv: 0.3-5.5 mU/l)	7	2.5	10.8	5	8.35	0.02	0.02	11.17	8.9
T4 (nv: 0.9-1.8 pmol/l)	1.2	1.1	1.2	1.3	1.3	1.6	1.6	1.53	3.13
T3 (nv: 2.6-5.1 pmol/l)								3.6	
Antibody antimicrosomal (vn: < 60 IU/l)	1,972	2,512	2,896					66	46

nv: normal value.

possible pathologies. On the other hand, the study in thyroid function confirmed the presence of high levels of thyroid antibodies (anti TPO: 1,972 UI/ml [normal <60]), high TSH and normal T4, which, associated with the neuropsychiatric symptoms and the lack of response to usual drug treatments, directed the diagnosis towards Hashimoto's encephalopathy.

Treatment was begun with steroids (methylprednisolone IV [1 g/day] for five days followed by prednisone per os [1 mg/kg/day], decreasing over 4 weeks) and the thyroxin dosage was doubled. The duration and intensity of the psychomotor agitation and aggressiveness decreased, but not the frequency. The rhythm of sleep became completely normal and the patients partially recovered his level of daily functioning, being able to follow previously established routines and enabling the carers to have improved control of his conduct. At present, he has received a second cycle of steroids to try to achieve the initial response to them, without any modification in the dosages of thyroxin, olanzapine (5 mg/8 h) and risperidone (1 mg/12 h).

Discussion

Analysing this case, we found symptoms compatible with a subacute presentation of neuropsychiatric disorders, which, associated with thyroiditis with thyroid function controlled with medication and a partially positive response to steroid treatment, were compatible with Hashimoto's encephalopathy. However, it is important not to discount the fact that the patient's underlying pathology —Down syndrome with autism and severe mental retardation– makes the symptoms described very difficult to characterize. The episodes of psychomotor agitation could be considered to respond to worse autistic behaviour at the start of adolescence. Furthermore, it is not easy to specify why the patient responds to steroids and not to antipsychotic or mood enhancing medication which were tried before.

The complimentary examinations do not provide conclusive data and are only necessary to rule out other aetiologies. The most characteristic findings in the analysis of cephalorachidian liquid (CRL) are one case of high protein levels (no higher than 100 mg/dl), one without pleocytosis, and oligoclonal bands, but the latter are only present in a few cases. Tomography and magnetic resonance imaging of the brain are normal in 75%of patients and a variety of non-specific abnormalities have been described such as cerebral atrophy, white matter lesions, abnormalities in the cortex and changes in the blood vessels. In the case reported here the cranial MR scan was normal and the CRL was not studied due to the absence of symptoms of infection and the subacute, fluctuating course of the neuropsychiatric manifestations.

The use of other techniques such as single photon emission computed tomography (SPECT) has reported normal studies but also cases of global or local hypoperfusion (at times with greater compromise of frontal lobe function). As for the electroencephalogram, it can be normal or have a non-specific abnormal pattern with a generalized slow wave (the most common), epileptiform abnormalities or photoparoxysmal responses.

It should be pointed out that despite the high prevalence of Hashimoto's thyroiditis described in the Down syndrome population, there are only 2 published cases of HE[5]. This could be due to difficulty mentioned earlier in recognising mainly psychiatric symptoms in patients who have previously shown cognitive-behavioural alterations. Furthermore, in patients with normal thyroid function, antibody testing is not routinely requested.

Compared with other autoimmune neurological disorders such as myasthenia gravis or paraneoplasia syndromes, in which the antibodies are involved in pathogenic mechanisms such as the blockage of neurotransmission or the disruption of cell signalling mechanisms, the role of antithyroid antibodies in the pathogenesis of Hashimoto's encephalopathy is not completely understood.

The onset of Hashimoto's thyroiditis is characterized by an increase in anti-TPO and/or anti-thyroglobulin antibodies, although no relationship has been found between the titre of the antibodies and the severity of the disease. The state of thyroid function is not decisive either. The presence of other positive antibodies (anti-NMDA, anti-thyroglobulin antinuclear) and of anti-TPO antibodies in up to 10%of the general population with no thyroiditis symptoms raises doubts about whether the latter is merely a marker or the physiopathological cause.

This encephalitis is usually described as responding well to steroids, but only 40%of patients have a complete effect and return to their baseline state. The lack of response to steroid treatment raises doubts about the diagnosis of the entity since the causal hypothesis is considered autoimmune. Several studies highlight the use of steroids and recommend them as a therapeutic option, as the disease is considered potentially reversible.

The suggested doses are 2-3 mg/kg/day of prednisone during the first month, followed by 1 mg/kg/day for 2 to 4 months until total recovery, and finally the dose is gradually reduced. Other immunosuppressive drugs could be used as an alternative in cases with side effects due to steroids, particularly for long term treatment[10]. In the case under study, the first cycle of steroids was relatively short (4 weeks) despite a partial improvement being seen, and for this reason a second cycle was given for a longer period of time.

The difficulty in diagnosing and treating Hashimoto's encephalopathy is due to: the variety of clinical manifestations; the fluctuating course of the disease (relapse-remission or continual progression); different structures of the CNS being affected to different degrees by the disease; the little evidence of a direct relationship between the state of thyroid function and the development of symptoms; and also the existence of many physiopathological processes involved which could be the cause. All this results in the disease still being hardly recognised[11].

These symptoms are referred to in order to include them in the differential diagnosis of patients with neuropsychiatric symptoms with subacute or fluctuating onset which do not respond to normal medication and in which other more common causes have been ruled out. This is even more relevant if there is an associated autoimmune pathology, as occurs frequently in children with Down syndrome. The arguments that uphold this suggestion are:

—Hashimoto's encephalopathy is an uncommon neurological disease and is thus little known and can go unnoticed, especially in the infant population, as its diagnosis depends on a high degree of clinical suspicion.
—Although it is associated with thyroiditis, it is not essential for there to be a hormone function disorder, and the antibodies can even become positive during the evolution of the disease. Thus, regular antibody testing is recommended in cases where this entity is suspected.
—There is an added difficulty for doctors when assessing and identifying the symptoms of this disease in patients with Down syndrome, as their behavioural profile is often difficult to interpret. All this makes us think that this disease is infra-diagnosed in patients with DS.
—Although there is no clear aetiopathogenesis, treatment with steroids or immunomodulators is effective, so this must be considered when this diagnosis is suspected, in order to try to benefit the greatest number of children.

The most relevant fact to reveal about this entity is that, despite being uncommon, there is a treatment option with a significant response rate. Therefore, when suspected, it is important to perform therapeutic testing, as the neuropsychiatric symptoms generate an important family and social dysfunction and even partial improvement is of great value to the patient's relatives and other people around them.

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