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**Case Report**

# CEREBRAL CAVERNOUS MALFORMATION COEXISTING WITH PITUITARY ADENOMA, HASHIMOTO THYROIDITIS AND MENTAL ILLNESS: FIRST CASE REPORT.

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**ABSTRACT**

Cerebral Cavernous Malformations (CCMs) are vascular lesions involving brain capillaries. They may occur sporadically or be inherited as autosomal dominant character. Due to incomplete penetrance, CCMs incidence is underestimated and, overall sporadic cases, are often accidentally diagnosed. Rarely CCMs are linked to other pathological conditions. Here we present the first case in literature of a young woman affected by sporadic CCM, pituitary adenoma, Hashimoto thyroiditis and mental illness of unknown etiology. Symptoms' analysis suggests that she may suffer of Hashimoto encephalopathy (HE), a condition that in very few cases develops together with Hashimoto thyroiditis. Genetic bases of HE are still unknown and symptomatology is very heterogeneous. This paper is a preliminary report of the case and is focused on complexity of clinical manifestations that makes the diagnosis uncertain. If our hypothesis will be confirmed by further analysis, our aim will be to clarify genetic causes of HE.



## 1. Introduction

Cerebral Cavernous Malformations (CCMs, OMIM #116860) consist of enlarged and tangled capillaries that usually develop at Central Nervous System (CNS) without involved brain parenchyma. Ultrastructural features include alterations at intercellular tight and adherens junctions and at cellular-extra cellular matrix (ECM) adhesions, and absence of pericytes. Abnormal angiogenesis is among the causes of CCMs. Phosphatidylinositol 3-kinase (PI3K)/Akt pathway play an important role in angiogenesis. Recent studies showed that PTEN, a tumor suppressor gene, is an antagonist regulator of the PI3K/Aktand MAPK pathwayas well as anegative regulator of the cell cycle by down-regulation of cyclin D1 [1].

CCMs' incidence was estimated to be up to 0,5% worldwide and represent about 20% of all cerebrovascular malformations. Clinical manifestations usually include intracerebral haemorrhage, seizures, headaches and focal neurological deficits. Diagnosis of cavernous angioma is usually confirmed by Magnetic Resonance Image (MRI) performed with "gradient-echo" sequences. Two forms of the pathology were described: i) sporadic that usually arises with single lesions among 30 and 50 years old, ii) familial, inherited with an autosomal dominant pattern, which often appears with multiple lesions already in childhood. Familial forms are characterized by incomplete penetrance and variable expressivity [2] and are linked to germline mutations at the three loci *CCM1/KRIT1* (7q21.2), *CCM2/MGC4607* (7p13) and *CCM3/PDCD10* (3q26.1). Over the last few years the spectrum of mutations has expanded through discovery of new mutations and/or polymorphisms especially in *CCM2*[3] and *CCM3*[4] genes whose effects were evaluated by functional studies and in silico analysis [5,6].

However, in the absence of CCM gene mutations also the increase of oxidative stress can contribute to CCM pathogenesis [7].

Association of CCM with psychiatric disorders is unusual and neurological symptoms are often tightly linked to lesions' localization. Moreover, to date no cases of CCMs coexisting with autoimmune syndromes are reported in literature. Here we describe a very complex case of a young woman affected by sporadic CCM, pituitary adenoma, Hashimoto thyroiditis (HT) and psychiatric illness of unknown etiological basis.

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## 2. Case presentation

A 32 years-old woman arrived to our observation due to reporting of a single CCM lesion in temporal area. Moreover, in her family no other member is suffering, so she was classified as sporadic case. However, during anamnesis was reported a very complex clinical picture characterized by psychiatric symptomatology, Hashimoto thyroiditis and a pituitary adenoma. The first psychiatric disorder arose at age of 10, following parental divorce. Six years later Hashimoto thyroiditis was diagnosed and, at the age of 19, magnetic resonance highlighted the CCM lesion and, two years later, the pituitary adenoma. Treatment of psychiatric symptoms has been started already in childhood however, have been repeatedly suspended due to allergic manifestations at anxiolytics and antipsychotics. Although new drugs were given, psychiatric disorders have been increasingly serious; electroencephalogram showed alterations of no-epileptogenic origin[8]. Table S1 summarizes all clinical symptoms of the proband and all given therapies. To date, diagnosis is of schizoaffective disorder with personality disturbance.

The girl arrived to our laboratory for molecular diagnosis of CCM so, direct sequencing of the three causative genes were performed on DNA isolated from peripheral blood. Coding exons and intron–exon boundaries of the three genes were screened using primers (available upon request) designed according to the CCM1, CCM2 and CCM3 published nucleotide sequence of GenBank (accession no. NG_012964.1, NG_016295.1 and NG_008158.1 respectively). PCR products were sequenced on 3500 Genetic Analyser (Applied Biosystems, CA, USA), using the Big Dye Terminator v3.1 chemistry, following manufacturer's procedures. As in most sporadic cases, no germ-line mutations were detected.

| Age | Clinical manifestations | Diagnosis | Treatment | Adverse Drug Reactions (ADRs) |
|---|---|---|---|---|
| 10 | Psychomotor agitation; severe headache | | | |
| 16 | | Hashimoto's thyroiditis | Amniolytic (Alprazolam) Suspended because of allergies | Hyperprolactinemia, hallucinations, aggressiveness, dysmenorrhea, reduced appetite, myasthenia |
| 19 | Acute joint rheumatism; Anoresia and bulimia; Hyperprolactinemia | MRI: cavernous angioma diagnosis in temporal area | | |
| 20 | Feverish episodes associated with strong headache | EEG: sharp waves in left temporal-occipital area. Clinical diagnosis: dissociative state | Amniolytic (Diazepam); Suspended because of allergies<br>Antipsychotic (promazine HCl) Suspended because of allergies<br>Anticonvulsant (valproic acid) | Behavioural disturbances, psychosis, hallucinations, aggressiveness, restlessness, irritability, anger<br>TSH increase,apathy<br>Hyponatremia, weight loss, hallucinations, aggressiveness, restlessness, irritability, attention disorder |
| 21 | Hearing disassociation; non-epileptogenic EEG alterations<br>Hyperpyrexia<br>Arterial thromboembolism<br>Hyponatremia | Pituitary adenoma;<br>Borderline personality disorder | Antipsychotics (risperidone, olanzapine, quetiapinefumarate, levomepromazine)<br>Amniolytic (lorazepam, deloreazepam)<br>Antidepressant (fluoxetine)<br>Anticonvulsant (valproic acid)<br>Antiepileptic (oxcarbazepine, clorazepam) | Parkinsonism, headache, sleep-wake disturbance, hyperprolactinemia, sedation<br>Hypotension, akathisia, anxiety, psychomotor agitation, depression<br>Hyponatremia, depression, aggressiveness, hallucinations, anger<br>Hyponatremia, insomnia, headache, hyperprolactinemia<br>Hyponatremia, weight loss, hallucinations, aggressiveness, restlessness, irritability, attention disorder; |
| 22 | Diffuse myalgia<br>Recurrent headache<br>Drowsiness<br>Chronic fatigue | Personality disturbance, asthenia and fatigability oh undiagnosed nature | Neuroleptic (Zuclopenthixol Dichlohydrate)<br>Sedative (triazolam)<br>Hormone replacement therapy (Levothyroxine sodium) | dizziness, diplopia, hyponatremia, asthenia, nausea, hallucinations, agitation, aggressiveness, anxiety, restlessness<br>Akathisia, drowsiness, myalgia<br>Amnesia, tachycardia, noises and light hyper-sensibility<br>Tachycardia, arrhythmias, headache, asthenia, cramps, pseudotumorcerebri, restlessness, insomnia, weight loss, agitation |
| 23 | Confusional state; psychomotor agitation; logorrhoea; restlessness;exalted mimicry; reduced attention span; memory alterations; unstable emotions; accelerated thinking; auditoryhallucinations;persecutory delusions | EEG: non-epileptogenic alterations;<br>iatrogenic alterations | Mood stabilizer (lithium carbonate) | Polydipsia, memory loss, convulsions, drowsiness, aphasia, parkinsonism, tremor, myasthenia, muscle stiffness, disorientation |
| 24 | Hearing disassociations<br>Rising dysphoria<br>Mood instability | Bipolar disorder with maniacal episodes | Anticonvulsant (valproic acid)<br>Amniolytic (deloreazepam)<br>Sedative (triazolam)<br>Hormone replacement therapy (Levothyroxine sodium) | As reported |
| 25 | Further psychotic disorders | Bipolar disorder, Disintegration of personality; Absence of functional autonomy | Antipsychotic (clozapine)<br>Anticonvulsant/antiepileptic (pregabalin) | Tachycardia, convulsions, drooling, loss of sphincters control, hypotension, neuroleptic malignant syndrome<br>Dizziness, asthenia, disorientation, weight gain |
| 26 | | Personality disorder in subject with cerebral cavernous malformation, with learning and attention difficulties | | |
| 29 | | Schizoaffective disorder with predominant positive symptomatology, disintegration of personality, absence of functional autonomy | | |

**Table 1 -** Clinical symptoms of the proband and all given therapies.

However, the case aroused our interest about the hypothesis of a common etiological basis for the complex clinical picture.

## 3. Discussion

CCM are benign lesion that affected capillaries of central nervous system leading to neurological clinical manifestations as focal deficits, seizuresand headaches. It however, psychiatric syndromes may also rarely occur. Conversely, is well known that HT influences mood and affective status [9]; moreover, many psychiatric disorder may have autoimmune origin. A rare encephalopathy condition, called Hashimoto encephalopathy (HE), results from excessive levels of antithyroid peroxidase antibodies (TPO Abs). Typical clinical manifestations of HE is psychiatric illness, characterized by seizures, psychosis, hallucinations, myoclonus, cognitive deficits and anti-epileptics and anti-psychotics resistance and usually occur before hypothyroidism. HE etiology is still unclear and it was reported both in adults and in children [10]. The case we examined is very complex and a specific clinical diagnosis has not yet been formulated.

On our opinion, this excessive psychiatric symptomatology is not consequence of CCM lesion, as initially suspected rather it is asymptomatic and was accidentally discovered during investigation to explain psychiatric disorder. Observed progressiveworsening, despite pharmacological treatment, could be due to adverse drug reactions (ADRs), being these similar to symptomatology. However, HE well matches with the clinical presentation observed in our proband, characterized by hallucinations, psychosis, myoclonus, anxiety, and restlessness. HE symptoms often appear earlier than hypothyroidism and are very heterogeneous. Patients are responsive to steroid therapy. To date, do not exist specific diagnostic criteria and EEG may show no alteration. The only diagnostic marker is hematic level of TPO Abs, usually much higher than normal physiological value. Actually, we don't have information about this data. However, hyperprolactinemia was constantly reported and may be consequence of pituitary adenoma.

## 4. Conclusions

The case here we reported is the first in literature in which a CCM lesion occurs together with pituitary adenoma, HT and supposed HE. Genetic causes of HE are still unknown, so we believe useful to deepen investigations focusing on whole genome study and epigenetic phenomena.

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