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Hypothalamic Hamartoma with Epilepsy and Psychiatric Symptoms: A Case Report

Yahya Amara[1*], Zineb Bencharfa[1], Nawar El Moussaoui[1], Siham Belbachir[2], Abderrazak Ouanass[2]

[1]MD, Ar-Razi University Psychiatric Hospital in Salé, Faculty of Medicine and Pharmacy, University Mohammed v from Rabat, Morocco
[2]Professor of Higher Education in Psychiatry, PhD, Ar-Razi University Psychiatric Hospital in Salé, Faculty of Medicine and Pharmacy, University Mohammed v from Rabat, Morocco

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***Corresponding author:** Yahya Amara
MD, Ar-Razi University Psychiatric Hospital in Salé, Faculty of Medicine and Pharmacy, University Mohammed v from Rabat, Morocco

Abstract **Case Report**

Introduction: Hypothalamic hamartomas (HH) are rare tumor malformations that can manifest as complex partial seizures refractory to anticonvulsants in adulthood and behavioral disturbances. The pathology can be misdiagnosed due to its rarity. ***Objectives:*** We attempt, from a clinical case, to alert neurologists and psychiatrists to the neurological and psychiatric symptoms of HH, knowing that they may encounter a very small number of these cases in their practice. ***Methods*:** We report the case of a 45-year-old man complaining of seizures manifested by falls, tonic spasms of the limbs and hypermotor activities. Her seizures began at the age of fifteen and presented as a deviated eye, followed by frequent seizures of varying frequency. The patient also had symptoms of intellectual disability. He was hospitalized in our psychiatry department for the management of a suicide attempt made in a hallucinatory setting, comorbid with drug-resistant epilepsy. ***Results:*** Neuroimaging concluded with the diagnosis of HH. The patient became a candidate for surgery after that. In our clinical case, the patient was able to benefit from a radio surgical treatment Gamma Knife (GK). ***Conclusion:*** In this case, the underlying etiology of the seizures and psychiatric manifestations was diagnosed thirty years after the onset of symptoms. Therefore, neurologists and psychiatrists should consider it in patients with suspicious signs and symptoms.

Keywords: Hypothalamic Hamartoma, Epilepsy, Psychiatric symptoms, Diagnosis, Gamma Knife.

1. INTRODUCTION

Hypothalamic hamartomas (HH) are rare benign congenital tumors arising from the ventral hypothalamus [1, 2]. HHs vary in size and site of attachment to the hypothalamus. Two clinico-anatomical phenotypes have been recognized. The parahypothalamic HHs (also called pedunculate) are attached to the anterior hypothalamus, usually in the region of the tuber cinereum and pituitary stalk, and are strongly associated with central precocious puberty [3, 4]. Conversely, intrahypothalamic (also called sessile) HHs attach posterior to the hypothalamus in the region of the mammillary bodies and are strongly associated with treatment-resistant epilepsy. Approximately 40% of HH patients have both refractory disorders epilepsy and central precocious puberty, usually with large HH lesions that attach both anteriorly and posteriorly to the hypothalamus [4].

HH-associated epilepsy has a progressive clinical course in 75% of patients, with the subsequent development of other treatment-resistant seizure types, including localized and generalized seizures [5, 6].

Psychiatric symptoms are well recognized (although less well studied) as a comorbid clinical feature of HH with epilepsy [5, 7, 8]. These can be disabling and represent the greatest challenge for the patient and their family. Externalizing behaviors with aggression and rage attacks are the most problematic psychiatric symptoms for patients with HH and epilepsy. Patients may have low frustration tolerance, with over-reactivity to relatively minor stimuli, sometimes with destructive and physically threatening characteristics.

2. METHODOLOGY

We performed a comprehensive chart review of the 45-year-old patient, with 1 year of pre-operative follow-up and 5-month post-operative follow-up at the time of writing this manuscript.

3. CASE PRESENTATION

We report the case of 45-year-old patient referred from the maxillofacial surgery department and admitted to our psychiatric hospital for treatment of a suicide attempt by throat cutting in a hallucinatory setting, in what appears to be schizophrenia evolving for twenty years associated with drug-resistant epilepsy. Psychiatric examination revealed delusional syndrome, hallucinatory syndrome and impaired judgment and insight. The patient also suffered from a mild intellectual disability.

His history of neurological pathology began when he was fifteen years old and included tonic-clonic epileptic seizures with varying frequencies that required neurologic follow-up. The patient received anticonvulsant treatment. No history of perinatal complications, head trauma or similar cases was noted in his family. The history of his psychiatric pathology also dates back to the age of fifteen, the patient had become isolated, insomniac, uttering delusional persecution centered on his relatives. He also had an intellectual disability. The patient has never consulted a psychiatrist before. No cause of the patient's pathology has been identified for more than thirty years, despite the fact that the patient underwent a number of radiological tests.

During his hospitalization the patient underwent complete biological and radiological examinations including Electroencephalogram (EEG), Cranial CT Scan and Cranial Magnetic resonance imaging (MRI). He was put on Amisulpride 800mg/day and Carbamazepine 800mg / day, with a slight distancing of his delirium and the regression of intrapsychic hallucinations, but without return to the premorbid state. MRI revealed hypothalamic hamartoma centered on the tuber cinereum.

Patient released from the hospital under antipsychotic and anticonvulsant treatment, and addressed in consultation of neurosurgery for ablation of the hypothalamic hamartoma. In our clinical case the patient was able to benefit from a radio surgical treatment Gamma Knife (GK) in a neurosurgical department.

3. DISCUSSION

Here, we describe a case with drug-resistant epilepsy that was treated for thirty years under the diagnosis of idiopathic generalized epilepsy. During his hospitalization in our psychiatric hospital structure for the management of a suicide attempt, the radiological assessment revealed hypothalamic hamartoma, and the patient became candidate for surgery.

The most common symptoms of HH, which are extremely rare benign tumors, include precocious puberty, gelastic epilepsy, and cognitive impairment [9, 10, 12]. Due to the extremely low incidence of HH many neurologists and psychiatrists see only a small number of cases throughout their careers [11-13]. As in the example we have described, this may cause delays in both diagnostic and treatment processes.

HH usually leads to seizures in early childhood, usually presenting with gelastic seizures [10, 11]. In our case, gelastic seizures were not reported either in childhood or later. Although gelastic seizures are known to be the hallmark of HH, a very small number of patients may experience other types of seizures such as tonic seizures [14]. Our patient also had this rare presentation of HH. No other epileptogenic source was identified in the patient's MRI or EEG and HH was the only result responsible for his seizures. The aggravation of childhood seizures in complex seizure disorders is reported in several cases of HH before [12], as was also observed in our patient. Mental disability is a common presentation of HH, especially in patients with early epileptic seizures [10]. Patients with HH are also known to have behavioral difficulties, including emotional instability, irritation, restlessness, and aggression. They may also develop attention deficit hyperactivity disorder, conduct disorder, learning disabilities, speech delay and anxiety [11, 15]. Our patient had a history of mild intellectual disability and had delusional persecution syndrome and intrapsychic hallucinations. Although less well studied, psychiatric symptoms are widely recognized as a coexisting clinical feature of HH with epilepsy [9]. These can be disabling, and they pose the biggest problem for the patient and their family. In our case, the intrapsychic hallucinations decreased after starting the antipsychotic treatment, with persistence of some delusional ideas of persecution centered on the entourage.

Biological mechanisms for aggression in patients with HH are unexplored. However, there is some circumstantial evidence available from anatomical considerations. HH lesions associated with epilepsy (and aggression) universally include attachment on or near the mammillary bodies in the posterior ventral hypothalamus [16]. Conversely, classical electrical stimulation experiments in feline models of aggression show that reactive (but not predatory) aggression localizes to the ventral hypothalamus in a zone that extends posteriorly to the level of the mammillary bodies [16]. Hypothesis-driven imaging studies examining differences between HH patients with and without aggression would be of interest [16]. The nature of synaptic connectivity (mediating the network connections for either aggression or epilepsy) between HH lesions and the hypothalamus remain unknown.

The medical treatment of these patients is generally unsuccessful [17]. Pharmacotherapy for psychiatric issues associated with HH is completely unexplored. However, a double-blind, randomized, placebo controlled trial of fluoxetine (a selective serotonin reuptake inhibitor) for intermittent explosive disorder (no subjects in this study were known to have

HH) demonstrated safety and efficacy, suggesting a therapeutic trial in the HH population would be of interest [18]. Therefore, surgical intervention remains the best solution [17]. In our clinical case the patient was able to benefit from a radio surgical treatment Gamma Knife (GK) in a neurosurgical department 5 months ago. GK seems to be an effective technique, in particular for small HHs located intraventricularly or in the floor of the third ventricle. The tight connections with the tracts and the optic chiasm, on the one hand, and the poor delineation of the upper part of the lesion, often difficult to distinguish from the healthy hypothalamus, on the other hand, present two challenges [17]. Régis *et al*., [19] performed the first multicenter study of GK treatment of HH (seven centers, ten patients). The average marginal dose administered was 15 Gray (Gy). Two patients had to be treated twice (after 10 and 49 months) because of insufficient efficacy. Our patient received a dose of 14 Gy. The authors only present the results for the eight patients who had more than a year of follow-up (from 12 to 71 months, with a median of 28 months). Two patients experienced rare seizures, two patients had more frequent seizures, and two patients had no seizures at all. The interval between the intervention and the disappearance of the seizures varies, usually lasting nine months [19]. Although there are few cases and a short follow-up period for these difficult-to-access lesions, GK appears to be an interesting strategy with very little morbidity.

In this reported case, the underlying etiology of the seizures and psychiatric manifestations was diagnosed thirty years after the onset of symptoms. Diagnosis could be reached earlier if clinical symptoms, patient history, EEG, and imaging findings were studied more precisely and keeping in mind HH as the etiology of drug-resistant epilepsy and psychiatric symptoms.

4. CONCLUSION

In conclusion, neurologists and even psychiatrists must consider the patient's history, typical clinical presentation of HH and evidence of HH on MRI in order not to compromise the health and functioning of the patient and to make the correct diagnosis. However, due to the extremely low prevalence of the disease and some of its outdated symptoms, these cases are susceptible to being misdiagnosed.

Abbreviations:

HH: Hypothalamic hamartomas
GK: Gamma Knife
EEG: Electroencephalogram
MRI: Magnetic resonance imaging.

Acknowledgements: Not applicable.

Machines used in this study

Electroencephalograms were obtained with BrainRT EEG System, manufactured by OSG, Belgium. Brain magnetic resonance imaging scans were obtained with magnetic resonance imaging system Philips Ingenia, manufactured by Philips, Netherlands.

Authors contributions:

YA was responsible of the patient recruitment, data collection, and literature review. ZB participated in the literature review besides that she wrote the manuscript with YA and NE. YA analyzed the data. SB and AO supervised the research overall and revised the manuscript.

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Availability of data and materials:

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DECLARATIONS

Ethics approval and consent to participate: There is no ethical issue.

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Competing interests: The authors declare that they do not have any competing interests.

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