CASE REPORT

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Familial Hemiplegic Migraine (FHM) with Transient Psychotic Symptoms: A Case Report and Literature Review

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ABSTRACT

Familial hemiplegic migraine (FHM) is a rare, autosomal dominant migraine syndrome characterized by transient hemiparesis and neurological symptoms. It is primarily associated with mutations in the CACNA1A, ATP1A2, and SCN1A genes, which disrupt neuronal excitability and contribute to complex clinical presentations. Although psychotic symptoms accompanying migraine attacks in FHM are exceedingly rare, they have been documented in a limited number of cases. This article presents a case of FHM diagnosed in a patient who exhibited transient psychotic symptoms during a migraine attack, with a focus on diagnostic and therapeutic approaches. The case is discussed in comparison to other rare instances reported in the literature. Psychotic symptoms in FHM are thought to arise from mechanisms such as cortical spreading depression and cerebral hypoperfusion. These symptoms are typically short-lived and respond rapidly to antipsychotic treatment. However, careful evaluation is essential to differentiate these episodes from primary psychotic disorders, thereby avoiding unnecessary prolonged antipsychotic use. This case underscores the importance of a thorough clinical assessment in FHM patients presenting with atypical psychiatric manifestations. The article aims to contribute to the understanding and management of psychotic symptoms in FHM, emphasizing the need for a multidisciplinary approach to diagnosis and treatment. Further research is warranted to elucidate the pathophysiology of psychosis in FHM and to optimize therapeutic strategies for this rare but clinically significant presentation.

Keywords: Case report, cortical spreading depression, familial hemiplegic migraine, psychotic disorders

INTRODUCTION

Some neurological disorders may manifest with mood changes, cognitive impairments or psychotic symptoms; psychiatric symptoms may be in the foreground in these clinical situations and may complicate the diagnostic process (Özer et al. 2014, Akıncı et al. 2017, Geniş and Coşar 2020). One of these diseases, hemiplegic migraine (HM), is a rare type of migraine with aura that starts at an early age and presents with neurological symptoms such as transient hemiparesis. The etiology and pathophysiology of HM, which accounts for less than 1% of migraine cases, is quite complex. Familial hemiplegic migraine (FHM) is a rare subtype of migraine and is characterized by transient hemiparesis during attacks (Pietrobon 2007). FHM shows autosomal dominant inheritance and may present with neurological and psychotic symptoms (Russell and Ducros 2011a).

FHM is associated with ion channel dysfunctions and is often linked to mutations in the CACNA1A, ATP1A2 and SCN1A genes (Di Stefano et al. 2020). These genes play critical roles in the regulation of neuronal ion channels and pump functions. The CACNA1A gene encodes the α1A subunit of P/Q-type voltage-dependent calcium channels (Indelicato et al. 2021); the ATP1A2 gene encodes the α2 subunit of the Na^+/K^+-ATPase pump (Carreño et al. 2013); and the SCN1A gene encodes the α1 subunit of voltage-dependent sodium channels. Mutations in these genes can lead to

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migraine attacks by affecting neuronal excitability (Grangeon et al. 2023). Mutation in the CACNA1A gene is classified as FHM Type 1, mutation in the ATP1A2 gene as FHM Type 2 and mutation in the SCN1A gene as FHM Type 3 (Russel and Ducros 2011).

The clinical presentation of familial hemiplegic migraine (FHM) is broad and psychotic symptoms have rarely been reported in patients during attacks (Table 1). In almost all of these cases, psychotic symptoms such as hallucinations and delusions accompanied the attack. This suggests that FHM may be associated with psychotic symptoms as well as neurological symptoms.

This article deals with psychotic symptoms during a migraine attack in a patient diagnosed with FHM. The fact that psychotic symptoms accompany the neurological side of hemiplegic migraine requires a multidisciplinary approach in diagnosis and treatment. With this case report, we aim to provide a perspective on the pathophysiological mechanisms underlying psychotic symptoms and discuss clinical management strategies for such complex cases in the light of the literature.

CASE

A 50-year-old man with known Hashimoto's thyroiditis, primary congenital glaucoma and migraine with aura presented to the emergency department with complaints of headache radiating from the nape of the neck to half of the head, numbness and weakness in the right arm and inability to speak. In his history obtained from his wife, it was learned that the patient started to feel numbness in his jaw and right arm 2 days ago and interpreted this condition as a precursor of migraine headache. One day after the onset of these symptoms, it was learned that he started to give meaningless answers to the questions that directed to him and he vomited four times in the last 12 hours before his emergency room admission. It was learned that he was admitted to the emergency department with complaints of weakness in his right arm, lisping in speech and impaired consciousness.

Neurologic examination that performed in the emergency department revealed that he was drowsy and partially coherent, he could obey single-step commands, visual examination could not be performed because of visual impairment due to primary congenital glaucoma, he could not speak and responded to questions with head movements. No nuchal rigidity was detected, sensory examination was normal and the right upper extremity was plegic.

Computed tomography (CT), CT angiography and magnetic resonance imaging (MRI) were performed to exclude cranial vascular pathologies. Decreased regional blood flow (hypoperfusion) was reported throughout the left cerebral hemisphere (Figure 1, 2, 3).

Table 1. Cases of Hemiplegic Migraine with Psychotic Symptoms in the Literature

Title	Number of Patients	Cases	Family History
Episodes of acute confusion or psychosis in familial hemiplegic migraine. (Feely MP et al, 1982	3	Different members of the same family were diagnosed with FHM and psychosis accompanying the attacks. 1. A 70-year-old female patient with HM presents with short-term motor deficits, confusion, dysphasia and psychiatric symptoms (hallucinations and delusions) that occur episodically and usually resolve within 24 hours. Similarly, in the past, motor deficits have been accompanied by confusion and then persecutory delusions lasting for 3 days. 2. A patient with a diagnosis of HM, accompanied by auditory and visual hallucinations, yellows and confusion A 3. Accompanied by psychotic symptoms and confusion (content not mentioned)	The patient's nephew The son of the patient's nephew 4th generation nephew
Familial hemiplegic migraine with cerebellar ataxia and paroxysmal psychosis. (Spranger et al, 1999)	2	5 members of the same family with CACNL1A4 gene mutation; 2 (46 y E and 42 y E) are accompanied by psychosis. Within 24 hours following the headache, patients experience colorful, moving, disturbing visual and auditory hallucinations, and persecutory delusions of being poisoned. It is accompanied by disorientation. Haloperidol is given, lasting 2 weeks.	Two sibling patients
Psychotic aura symptoms in familial hemiplegic migraine type 2 (Barros et al, 2012)	2	1. 48 years old, male, each episode with psychotic symptoms of time travel and accompanying motor deficits and aphasia. 2. 38 years old, female, admitted to a psychiatric clinic with right facial paralysis and dysphasia, with delusions that she can travel through time and that she will be harmed because of this ability. Cranial MRI and EEG are reported normal. After 48 hours, all symptoms disappear. Not on antipsychotics after discharge. Only hemiplegic migraine attacks, psychosis does not recur.	Two patients from the same family
Familial Hemiplegic Migraine and Recurrent Episodes of Psychosis: A Case Report. (LaBianca et al, 2015)	2	1. 70 years old, male, migraine attacks every 6 months since his youth, with unilateral sensory symptoms of blurred and numb eyes, 25% developing hemiplegia. He has 9 episodes of confusion and psychosis in 23 years. It occurs during or within 2 days of a headache. He has psychotic symptoms such as seeing a chainsaw on the ceiling, smoke coming from his legs, voices making comments, seeing someone in the room. 2. 44 years old, male, diagnosed with hemiplegic migraine, 4 times confusion and psychosis.	Two cases of father and son

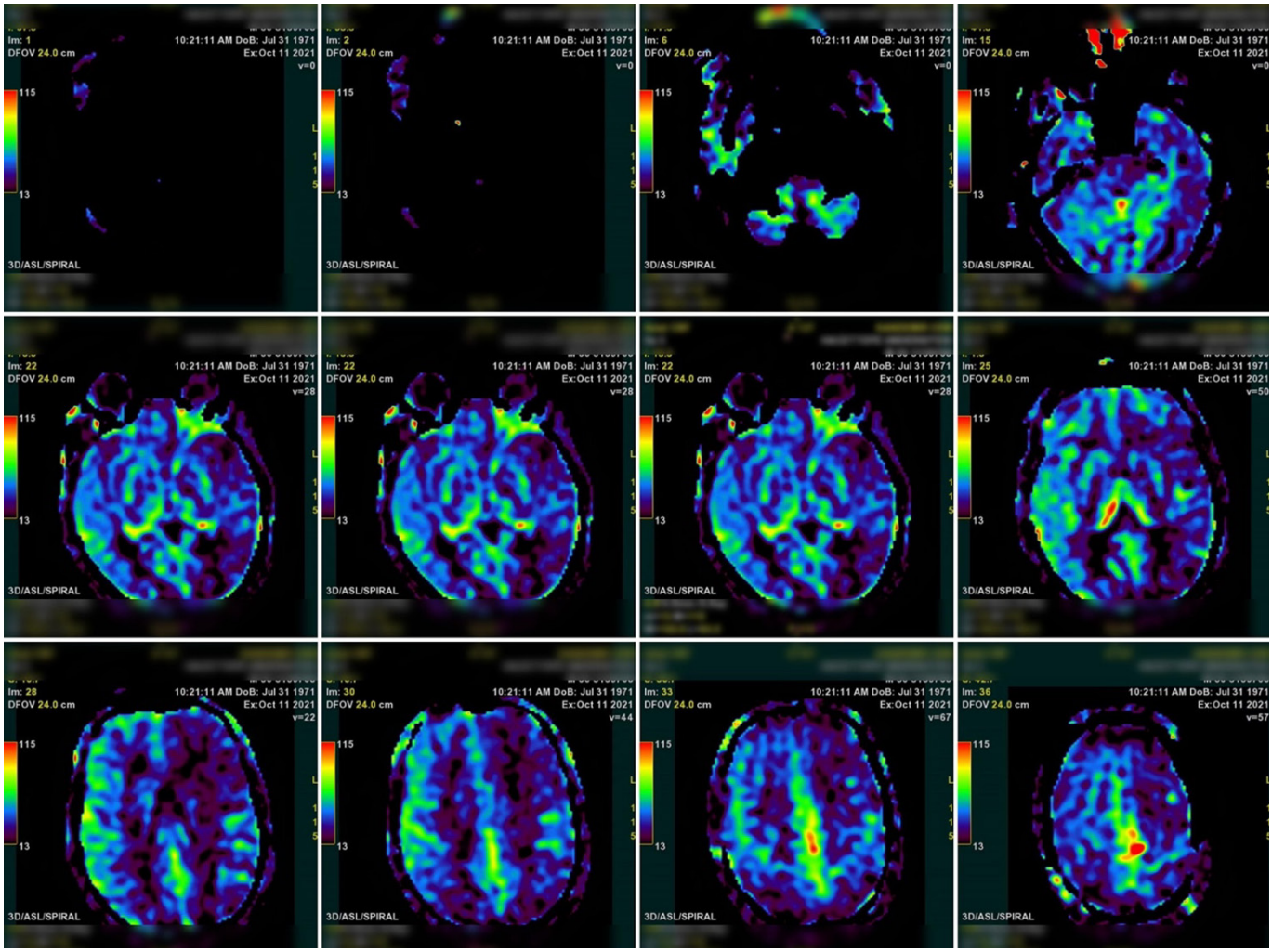

Figure 1. Magnetic resonance perfusion imaging of cerebral arterial spin labeling (ALS): Hypoperfusion (CBF) in the left cerebral hemisphere.

The patient was consulted to the infectious diseases unit and a lumbar puncture was performed because his body temperature was 38.2°C and he was unconscious on admission. Cerebrospinal fluid (CSF) biochemistry and culture results were reported normal and infectious causes were excluded. The COVID-19 test was negative and the thorax CT result was reported as normal. Electroencephalography (EEG) performed due to altered consciousness was reported as mild to moderate ground activity irregularity characterized by diffuse slow waves at theta frequency, more prominent on the left side, and epileptiform anomaly characterized by slow, sharp and spike activities at theta frequency in bilateral posterior temporal and occipital regions. The patient was hospitalized with ischemic attack, postictal symptoms and hemiplegic migraine. Levetiracetam 2000 mg/g, lamotrigine 50 mg/g, acetylsalicylic acid 100 mg/g were started.

On the 2nd day of admission, neurologic examination revealed improvement in speech and motor weakness. The patient, who was followed up in the neurology clinic, had hallucinations of seeing and talking to people who were not in the room 4 days after admission, guilt delusions that he had killed someone he did not know and persecution delusions that he would be harmed by the relatives of this person. The patient was evaluated by psychiatry clinic and it was learned that he had not had these complaints before. It was thought that the patient did not benefit from the ketiapine 25 mg/g and haloperidol 2 mg/g treatments initiated by neurology and olanzapine 5 mg/g was started. The patient's psychotic symptoms improved within 48 hours. The patient's psychotic symptoms completely regressed and treatment was reduced to olanzapine 2.5 mg/g on day 10 and completely discontinued on day 20. The patient was diagnosed with hemiplegic migraine by the neurology department.

The patient was evaluated in the psychiatry outpatient clinic after discharge and it was learned that he had headaches that started during his university years, occurred once a month, were usually unilateral, started from the nape of the neck and radiated to one side of the face and lasted for 1-2 hours, and

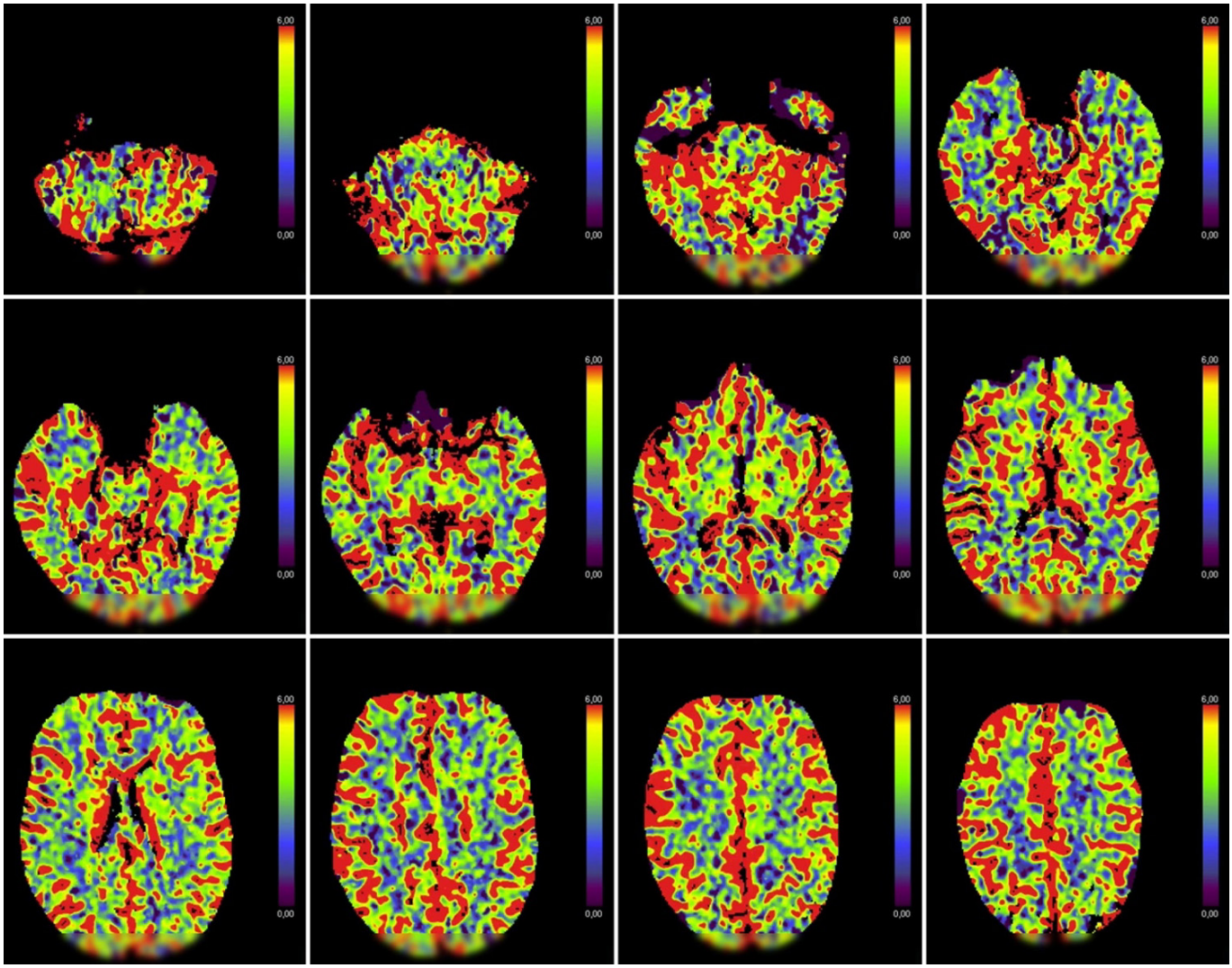

Figure 2. Computed tomography perfusion imaging of the brain: Hypoperfusion (CBF) in the left cerebral hemisphere.

these attacks resolved with nonsteroidal anti-inflammatory drugs. From the same period onwards, recurrent attacks recurring 1-2 times a year with different characteristics have also developed; these attacks, which are characterized by paresthesias starting in the right arm and spreading to the tongue and ipsilateral body half, followed by same-sided motor weakness, speech impairment, headache and marked desire to sleep, usually last for 4-6 hours, and in some cases up to 24 hours. He was diagnosed as "migraine" in the neurology clinic and valproic acid treatment was started. However, the patient discontinued the medication on his own initiative without a physician's recommendation because the attacks became more frequent despite the treatment. It was reported that in some previous migraine attacks, he experienced hallucinations of vivid colors and seeing people he did not know, these symptoms resolved spontaneously within a few hours and he did not use any medication for these conditions; the last attack of a similar nature occurred approximately two years ago.

In the family history of the patient, it was learned that his father and brother were diagnosed with migraine, and this was shown with the family tree (Figure 4). It was reported that his brother's migraine attacks started with unilateral sensory symptoms, occasionally progressed with hemiplegia, were accompanied by psychotic symptoms and confusion in only one of these attacks, recurred approximately every two months, and he used valproic acid prophylactically. It was reported that the father experienced migraine attacks occurring once a year, similar to that of the patient, with auras starting with unilateral numbness and accompanying hemiplegia; neuropsychiatric symptoms such as self-talk, meaningless answers to questions, inappropriate laughter and confusion were observed during these periods, but he did not remember these symptoms after the attack. It was learned that the father was on lamotrigine.

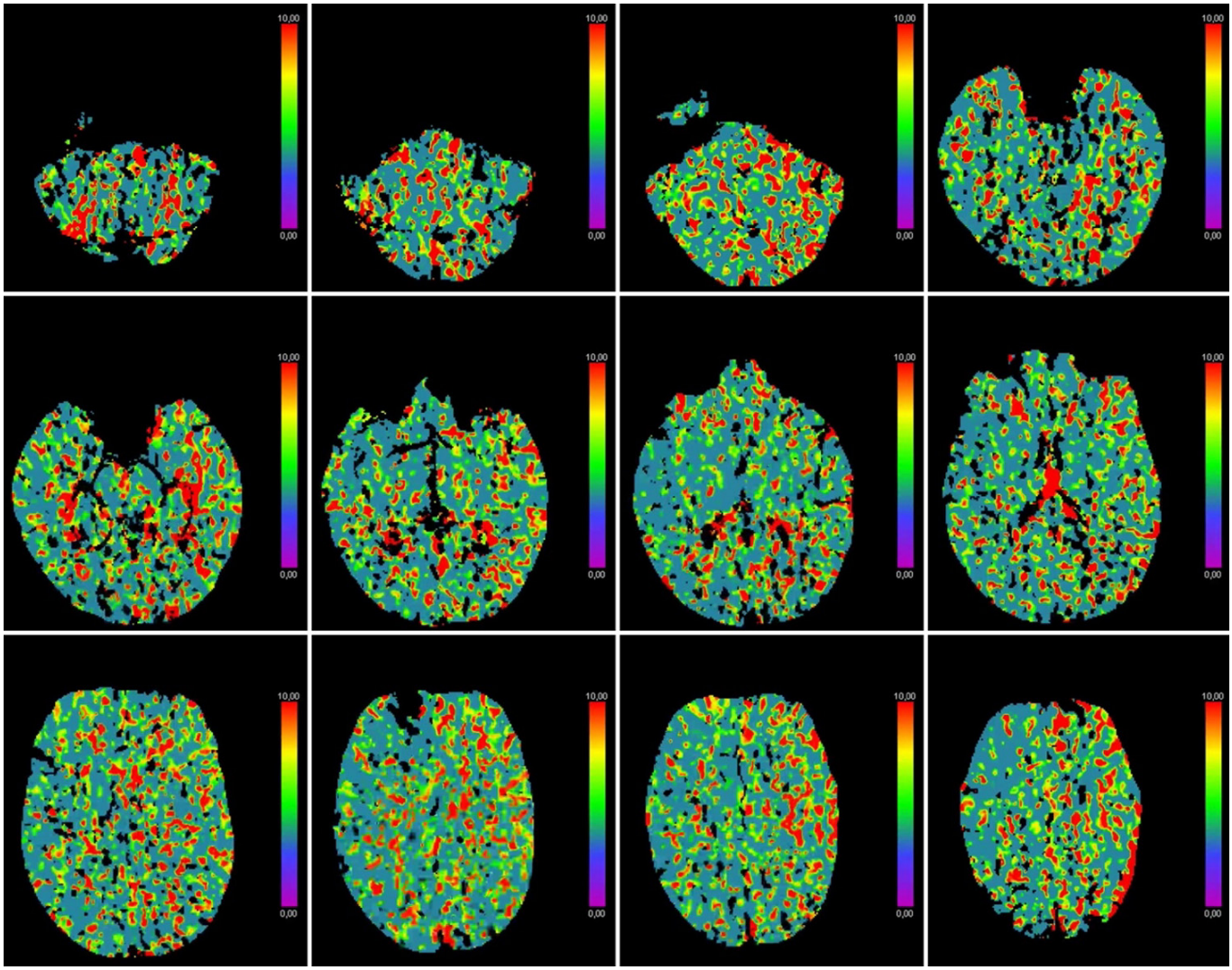

Figure 3. Computed tomography perfusion imaging of the brain: Increased blood mean transit time (MTT).

DISCUSSION

In this case, we present a rare presentation of both neurologic and psychiatric symptoms in a patient diagnosed with hemiplegic migraine. Hemiplegic migraine has been described as a special form of migraine with aura and is characterized by neurological symptoms such as transient hemiparesis. Familial hemiplegic migraine has a more complex clinical picture with autosomal dominant inheritance and usually early onset (Russell and Ducros 2011b). Although the accompaniment of psychiatric symptoms is rare in these patients, a limited number of cases have been reported in the literature in which psychotic symptoms may occur during the course of the disease (Table 1).

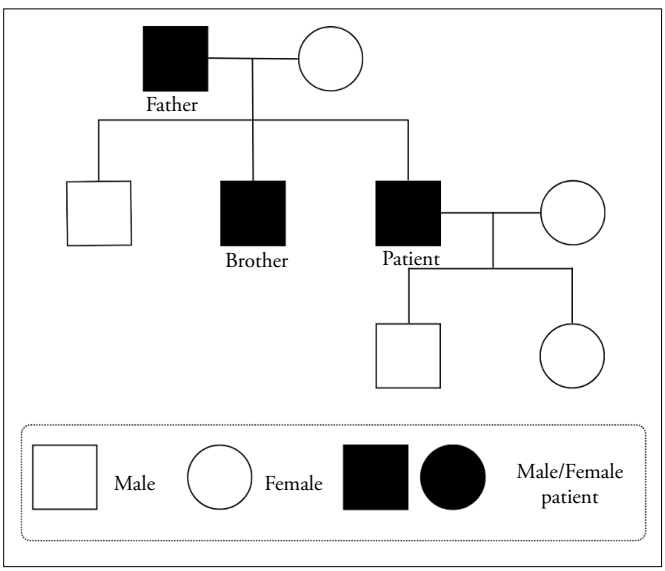

Figure 4. Family tree.

In the study of Feely et al. (1982) presented in the table, it was reported that a 70-year-old FHM patient developed psychotic symptoms such as visual and auditory hallucinations with headache, and these symptoms followed a course similar to delirium. Similarly, Spranger et al. (1999) reported that in a family carrying CACNA1A gene mutation, symptoms such as short-term but intense visual and auditory hallucinations, persecution delusions and altered consciousness occurred following headache. These cases, as in our case, present a clinical picture in which psychotic symptoms become prominent during a headache-related attack and completely resolve within a few days.

A similar picture was observed in the cases presented by Barros et al (2012). In this case, psychotic symptoms characterized by idiosyncratic, intense delusions during migraine attacks were observed in two patients with FHM. For example, one patient had delusions of being able to "travel in time", while another had paranoid thoughts and aggressive behavior towards others. Similar to our case, the fact that intense hallucinations and persecution delusions were observed during the attack suggests that these psychotic symptoms may be a special clinical feature associated with FHM.

In terms of the onset and course of psychotic symptoms, these cases should be handled from a neuropsychiatric perspective. The pathophysiology of psychotic symptoms associated with FHM can be characterized by both a "prolonged aura" and a delirium-like clinic. This distinction is difficult to make as the neuropathologic mechanisms of both conditions are not fully understood. Prolonged aura is a rare but serious neuropsychiatric complication of migraine characterized by aura symptoms that persist for a long period of time, exceeding the typical duration of 5-60 minutes without any infarct findings on neuroimaging (Chen et al. 2011). In the differential diagnosis of prolonged aura, cerebral and retinal infarcts, structural brain lesions, epilepsy and psychiatric disorders should be excluded; mechanisms such as cortical spreading depression (CSD) and cerebral vasoconstriction are thought to play a role in its pathophysiology (Severino and Green 2025). Cortical spreading depression is characterized by the generation of a slow-moving spontaneous depolarization wave (approximately 3-5 mm/min) over the cerebral cortex and transient suppression of neuronal activity (depression) in the cortical region where the wave passes (Charles and Baca 2013). (Charles and Baca 2013). It has been suggested that cortical spreading depression may extend to subcortical/limbic structures associated with consciousness (formatio reticularis) and psychotic symptoms (Russell and Ducros 2011b, Harriott et al. 2019). In particular, it has been previously reported that disturbance of consciousness and psychotic symptoms during prolonged aura can last for several days to weeks (Feely et al. 1982, Barros et al. 2012). This is consistent with the changes in consciousness, hallucinations and delusions observed in our case.

Another explanation is that these symptoms may be associated with delirium. Delirium is characterized by sudden onset, fluctuating changes in consciousness, psychomotor disturbances and psychiatric symptoms. Neuroimaging of the patient showed left cerebral hypoperfusion and increased mean blood flow time (Figure 1, 2, 3). Ischemia, postictal period and hemiplegic migraine are clinical conditions that can lead to cerebral hypoperfusion in the affected brain regions (Hansen et al. 2011, Rupprecht et al. 2010). It has been suggested that cerebral hypoperfusion and CSD caused by hemiplegic migraine may trigger energy deficiency, hypoxia and decreased cholinergic transmission and this may predispose to delirium (Spranger et al. 1999). As in our case, acute onset symptoms, altered consciousness and psychotic symptoms support a strong association with delirium. However, the diagnosis is based on clinical data and the lack of specific biomarkers makes differential diagnosis difficult.

In terms of treatment, olanzapine used in our case was chosen for the relief of psychotic symptoms and behavioral control and treatment was not continued for a long time. The efficacy of treatment suggests that atypical antipsychotics may be useful in such cases. While haloperidol has been reported to be effective in the prevention and management of delirium in the literature (Barros et al. 2012), it has been pointed out that drugs with anticholinergic effects may worsen delirium. In a case presented by LaBianca et al. (2015), levomepromazine was used for sedative purposes in combination with diazepam to be used when necessary during a migraine attack. It was stated that levomepromazine was preferred because of its sedation effect rather than its antipsychotic effect and that this preference was based on the experience of the neurologist who planned the treatment to use the drug frequently during the detoxification process. Based on both the limited reported cases and our case, it can be said that psychotic symptoms associated with FHM are usually short-term and respond to antipsychotics. However, such cases should be well evaluated in terms of the dose and duration of antipsychotic treatment. Longer than necessary use of antipsychotics may lead to side effects, the perception of a primary psychotic disorder and stigmatization.

In conclusion, this case reports a rare psychotic clinic of FHM and demonstrates that psychotic symptoms may occur during a migraine attack and these symptoms may follow a transient, delirium-like course. A multidisciplinary approach is of great importance in the diagnosis and treatment of FHM. A cross-sectional assessment may lead to a misdiagnosis of psychotic disorder, which may lead to unnecessary long-term antipsychotic treatment. In these cases, careful consideration of family history increases the accuracy of the diagnosis and

optimizes the treatment process. Further research is needed to better understand the pathophysiology and improve the clinical management of psychotic symptoms associated with FHM.

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