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MAIN TRIGGER FACTORS AND CLINICAL COURSE CHARACTERISTICS IDENTIFIED IN A LOCAL COHORT OF PATIENTS WITH CALL-FLEMING SYNDROME

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Abstract. *This study analyzed the principal trigger factors and clinical course of Call-Fleming syndrome in a local cohort. The study included 30 consecutive patients observed in the 1st and 2nd Neurology Departments of the Andijan State Medical Institute Clinic from October 2023 to December 2025. The design was prospective, single-center, and observational. Clinical, anamnestic, neurological, and neuroimaging data were evaluated systematically. Women predominated in the cohort: 23 of 30 patients (76.7%) were female, and 9 patients (30.0%) were in the postpartum period. The mean age was 38.6±9.4 years. Thunderclap headache was the leading clinical sign and was recorded in 29 patients (96.7%), while recurrent thunderclap attacks were documented in 27 patients (90.0%). A headache-dominant phenotype was observed in 18 cases (60.0%), a focal neurological phenotype in 7 cases (23.3%), and a complicated phenotype in 5 cases (16.7%). The most frequent triggers were vasoactive or serotonergic drugs in 12 patients (40.0%) and postpartum or hormonal factors in 9 patients (30.0%). Emotional stress and physical exertion were each identified in 5 patients (16.67%), while Valsalva-related situations or sexual activity were found in 4 cases (13.33%). Multiple triggers were present in 6 patients (20.0%), supporting the multifactorial nature of the syndrome. In this local cohort, Call-Fleming syndrome most often affected women of reproductive age and was characterized by recurrent thunderclap headache, frequent drug-related and postpartum triggers, and clinically heterogeneous presentation.*

Keywords: *Call-Fleming syndrome, reversible cerebral vasoconstriction syndrome, thunderclap headache, trigger factors, clinical phenotype, postpartum period.*

Introduction

Call-Fleming syndrome, also known as reversible cerebral vasoconstriction syndrome, is a clinical-radiological disorder characterized by multifocal and reversible narrowing of intracranial arteries. Its most typical manifestation is a sudden, severe, thunderclap headache. In a proportion of cases the syndrome may be accompanied by focal neurological deficits, seizures, confusion, convexity subarachnoid hemorrhage, ischemic lesions, or posterior reversible encephalopathy syndrome. Early recognition is therefore essential because the condition may mimic several acute cerebrovascular and inflammatory disorders.

A major diagnostic difficulty is the dynamic nature of the syndrome. Initial vascular imaging can be normal or only minimally informative, whereas vasoconstriction may become more evident on repeat studies performed days or weeks later. For this reason, a careful evaluation of anamnestic triggers and of the clinical phenotype is central to early diagnosis. The present article focuses on the local cohort profile of the syndrome, with special emphasis on the most relevant trigger factors and the leading clinical patterns.

Materials and Methods

This prospective single-center observational cohort study was performed at the 1st and 2nd Neurology Departments of the Andijan State Medical Institute Clinic from October 2023 through December 2025. Thirty patients with a diagnosis of Call-Fleming syndrome were included consecutively. The diagnosis was based on clinical presentation and paraclinical or neuroimaging data.

Eligible patients were hospitalized adults with available history and at least one neuroimaging examination. Patients with aneurysmal subarachnoid hemorrhage, primary angiitis of the central nervous system, cerebral venous sinus thrombosis, or incomplete data were excluded. For each case, the following variables were recorded: age, sex, reproductive status, postpartum state, trigger factors, headache characteristics, associated neurological symptoms, and neuroimaging findings.

The main triggers were grouped as follows: vasoactive or serotonergic medications; postpartum or hormonal factors; emotional stress; physical exertion; Valsalva-related situations or sexual activity; psychoactive substances; and unidentified triggers. Clinical phenotypes were classified into headache-dominant, focal neurological, and complicated forms. Neuroimaging results were analyzed for segmental or multifocal vasoconstriction, reversibility, and complications.

Results

The study population was predominantly female. Of the 30 patients, 23 (76.7%) were women, and 9 (30.0%) were in the postpartum period. The mean age of the cohort was 38.6±9.4 years, indicating that the syndrome mainly affected women of reproductive age in the local cohort.

The clinical core of the syndrome was thunderclap headache. It was documented in 29 patients (96.7%), whereas recurrent thunderclap attacks were observed in 27 patients (90.0%).

Nausea and or vomiting occurred in 15 cases (50.0%), photophobia or autonomic discomfort in 12 (40.0%), focal neurological deficit in 7 (23.3%), seizures in 4 (13.3%), confusion in 5 (16.6%), and cognitive complaints in 3 (10.0%).

Three major clinical phenotypes were identified. A headache-dominant form was present in 18 patients (60.0%) and represented the largest group. A focal neurological form was found in 7 patients (23.3%). A complicated form, including patients with a more severe clinical or radiological course, was present in 5 cases (16.7%). These findings show that although the classic cephalgic form predominated, a substantial proportion of patients had focal or complicated presentations.

Trigger analysis demonstrated that the most frequent precipitating factor was the use of vasoactive or serotonergic drugs, identified in 12 patients (40.0%). Postpartum or hormonal factors ranked second and were found in 9 patients (30.0%). Emotional stress and physical exertion were each recorded in 5 cases (16.67%), while Valsalva-related situations or sexual activity were observed in 4 cases (13.33%). Psychoactive-substance-related trigger was noted in 1 patient (3.33%), and no definite trigger could be established in 3 cases (10.0%). Importantly, 6 patients (20.0%) had more than one trigger simultaneously.

Neuroimaging findings supported the diagnosis in most patients. Segmental or multifocal vasoconstriction was identified in 24 patients (80.0%), and radiological regression or reversibility

was documented in 22 (73.3%). One patient (3.33%) had posterior reversible encephalopathy syndrome, 1 patient (3.33%) had convexity subarachnoid hemorrhage, and 2 patients (6.66%) showed infarction or ischemic lesions. In 3 cases (10.0%), neuroimaging was negative or inconclusive.

The relationship between phenotype and neuroimaging was clinically meaningful. Among the 18 headache-dominant cases, 16 showed isolated vasoconstriction. Among the 7 focal neurological cases, 5 also had isolated vasoconstriction. Among the 5 complicated cases, 3 had complicated neuroimaging findings. Thus, the proportion of radiological complications increased with clinical severity.

Discussion

The results indicate that the local cohort generally corresponds to the classical description of Call-Fleming syndrome. Recurrent thunderclap headache remained the most important clinical marker. From a practical point of view, this pattern helps distinguish the syndrome from ordinary migraine or nonspecific acute headache, especially when the onset is abrupt and the attacks recur over a short period.

The predominance of vasoactive or serotonergic medications among triggers is one of the most important practical observations of the present study. It emphasizes the need for focused history taking regarding recently used medications. The high proportion of postpartum and hormonal triggers likewise underlines the importance of considering the syndrome in women of reproductive age, particularly in the postpartum period.

The coexistence of emotional stress, physical exertion, and Valsalva-related situations, as well as the presence of multiple triggers in one fifth of patients, supports the multifactorial nature of the syndrome. The phenotype analysis further shows that the disease should not be regarded as a purely benign headache disorder. Focal deficits, seizures, confusion, and complicated neuroimaging findings require closer monitoring and more active management.

The main limitation of the study is its single-center design and relatively small sample size.

Nevertheless, given the clinical importance and frequent under-recognition of the syndrome, the systematic assessment of a local cohort provides useful diagnostic and practical information.

Conclusion

In this local cohort, Call-Fleming syndrome occurred predominantly in women, particularly in those of reproductive age and in the postpartum period. The leading clinical sign was recurrent thunderclap headache. The most important trigger factors were vasoactive or serotonergic medications and postpartum or hormonal conditions. Emotional stress, physical exertion, and Valsalva-related situations also played a meaningful role. The coexistence of several triggers and the increasing frequency of complicated neuroimaging findings in more severe phenotypes indicate that the syndrome is multifactorial and clinically heterogeneous.

Practical Recommendations

• Call-Fleming syndrome should be included in the differential diagnosis of every patient presenting with thunderclap headache, especially women of reproductive age and postpartum patients.

• History taking should specifically address recent use of vasoactive or serotonergic medications, emotional stress, physical exertion, Valsalva-related situations, and sexual activity.

• If initial vascular imaging is normal but clinical suspicion remains high, repeat neurovascular imaging should be planned because of the dynamic nature of the syndrome.

• Patients with focal deficits, seizures, confusion, or complicated neuroimaging findings should be considered high-risk and monitored more closely.

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