Autopsy CaseReports

Migrainous infarction: a rare and often overlooked diagnosis

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ABSTRACT

Migraine is a neurological entity and a well-known independent risk factor for cerebral infarction, which mostly afflicts the young female population. Researching focal neurological signs in this subset of the population with the diagnosis of a neurological ischemic event should always take into account the migraine as the etiology or as an associated factor. The etiology of central nervous system (CNS) ischemia is considerable. Migraine, although rare, also may be included in this vast etiological range, which is called migrainous infarction. In this setting, the diagnostic criteria required for this diagnosis is extensive. Herein, we present the case of a female adolescent who submitted to the emergency facility complaining of diplopia, dysarthria, and imbalance, which started concomitantly with a migrainous crisis with aura—a challenging clinical case that required extensive research to address all possible differential diagnoses.

Keywords
Migraine Disorders; Stroke; Internuclear Ophthalmoplegia

CASE REPORT

A 16-year-old female patient was admitted to the emergency unit complaining of a pulsatile, frontal headache over the last 12 hours accompanied by nausea with photo- and phonophobia. The symptoms evolved with diplopia, difficulty in performing adduction of the right eye, and dysarthria; imbalance started subtly about 1 hour after the onset of pain. The patient reported that at the beginning of the symptoms she presented partial loss of vision on the lateral field of the right eye, scotomas, and blurry vision, which lasted about 30 minutes, with spontaneous resolution. She denied fever or any other neurological complaint, or the use of oral contraceptives. She took dipyrone before going to the emergency department. Her medical history included the diagnosis of migraine that started with

the menarche at the age of 10 years, when she began presenting premenstrual migraine of variable intensity with visual aura, with predominant laterality also variable. The previous aura was characterized from scotomas, blurred vision, tunnel vision, and partial loss of vision, which was always reversible, with a maximum duration of 60 minutes. The patient did not remember having presented symptoms like diplopia or ataxia during previous events.

The physical examination revealed tachycardia, blood pressure of 150/80 mmHg, and a normal temperature. The neurologic examination revealed a wakeful, vigilant, and cooperative patient. Visual acuity was normal and without alterations on the field of vision; her pupils were isochoric and the direct response,

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the consensual response, and the accommodation of the pupils were normal. Paresis of the right eye when looking to the left was present (Figure 1), as well as diplopia, and a slow saccadic movement of the left eye in abduction, with horizontal nystagmus with the preservation of ocular convergence. Other cranial nerves presented normal function. Strength, sensitivity, and deep reflexes were preserved and symmetric. At the examination of station when the patient's feet were close together, she swayed backward, which was slightly worsened when she closed her eyes. Her gait was ataxic and she had a fall tendency to the left. Diadochokinesis, appendicular movement speed, and the finger-to-nose test were normal, but the heel-shin test was dysmetric at the left side. Other systems showed no abnormalities.

No improvement in the neurologic examination was noted after the patient was medicated with metoclopramide, ketoprofen, and dexamethasone; however, the pain and nausea did cease. The patient was hospitalized and submitted to a thorough etiological investigation.

The cerebral computed tomography (CT) and the angiotomography were normal. On the second day of hospitalization, a partial improvement of the symptoms was noted, but the diplopia remained steady. The cerebral magnetic resonance imaging (MRI) showed a focus of diffusional restriction in the paramedian right dorsal portion of the midbrain, which was consistent with the topography of the ipsilateral medial longitudinal fasciculus, without significant expansive effect, exhibiting hyperintense focus in T2 and fluid-attenuated inversion recovery (FLAIR), which did not show impregnation by the contrast medium (Figure 2). The cerebral (Figure 3)

and cervical MRI angiography and the cerebrospinal fluid analysis with protein electrophoresis were normal. The electrocardiogram (ECG), echocardiogram, and Holter ECG were normal. Biochemical analysis and thyroid function tests were normal. Antinuclear antibodies (ANA) was positive 1/640 exhibiting a fine nuclear dot pattern. However, antibodies anti-SS-B/LA, anti-SS-A/Ro, anti-SM, anti-double strain DNA, anti-neutrophil cytoplasmic antibody, and lupus anticoagulant tests were negative. Complement fractions C3 and C4 were normal. Anti-HIV, HBsAg, and anti-hepatitis C virus were negative. Acute phase proteins, serum lactate, and muscle enzymes were normal. The serum dosage of protein C, homocysteine, and antithrombin III tests were normal. The search for factor V Leiden was negative.

Thus, the clinical features, the imaging examinations, and the thorough investigation were consistent with the diagnosis of cerebral infarction without any risk factor other than migraine. The patient was prescribed salicylates and propranolol with gradual improvement. She was referred to an outpatient clinic for follow-up.

DISCUSSION

The interpretation of the physical examination, the laboratory testing, and the imaging, renders the conclusion of an internuclear ophthalmoparesis (INO) of ischemic origin.

INO is a syndrome derived from the medial longitudinal fasciculus (MLF) injury. The MLF is a set of myelinated fibers that extends along the entire brainstem and the spinal cord.[1,2] These fibers present a varied origin and destiny in their paths and stand as


Figure 1. Paresis of the right eye when looking to the left.

an integration tool. In the pons and the midbrain, the MLF stays close to the midline, ventrally to the fourth ventricle and the cerebral aqueduct. The center of the conjugate gaze lies between the dorsal pons and the mesencephalic tegmentum where the MLF harbors the internuclear fibers of the sixth and third cranial nerves.[3] Diplopia is an important symptom of INO, but in mild lesions it may present as a visual blur, which is unleashed when the conjugate gaze is directed towards the opposite side of the injured eye, or during the adduction of the affected eye.[3]

The most frequent causes of INO are cerebrovascular diseases in elderly patients, and demyelinating diseases, which mostly afflict the younger female patients.[3-5]

The other clinical features of our patient, which are consistent with INO and lead to anatomic localization are: (i) normal eye convergence (since the fibers responsible for the convergence are cranially located in the midbrain); (ii) nystagmus in adduction of the non-paretic eye;[6] and (iii) sensitive and/or motor dysmetria on the left inferior limb.[3]

As shown in the MRI (Figure 2), the ischemia is located in the highly concentrated area of motor-related
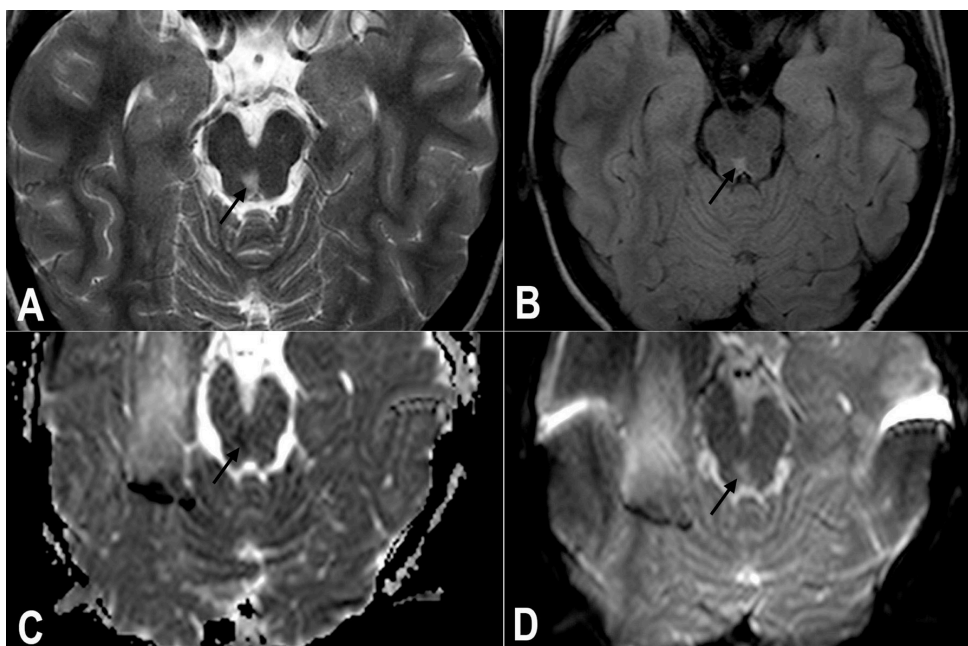
Figure 2. Brain MRI – Axial T2-weighted (**A**) and FLAIR (**B**) showing hyperintensity focus in the right periaqueductal region of the midbrain (black arrow). Axial ADC map (**C**) and DWI (**D**) show ischemic insult characterized by the restriction of free water molecules in the same region of the midbrain (black arrow). ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery sequence; MRI = magnetic resonance imaging.
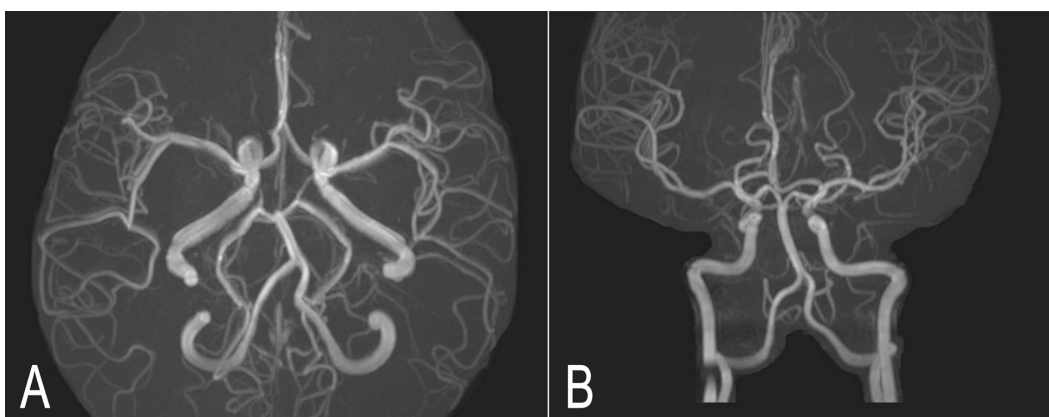
Figure 3. Cerebral magnetic resonance angiography (3D reconstructions). Oblique axial (**A**) and oblique coronal (**B**) images show normal intracranial arteries.

pathways, such as the rubrospinal tract, the medial lemniscus, and the pontocerebellar and tectospinal fibers of head adjustment to cocleo-vestibular stimuli. Therefore, motor and sensitive ataxia may be present if the area of ischemia is large enough.[1]

The cause of cerebral ischemia in children and young adults substantially differs from that of the adult/elderly population.[7] Acute ischemic stroke accounts for approximately 50% of all strokes in children.[8] The incidence among children is low and varies according to race (2.6/100,000 white children and 3.1/100,000 black children).[9]

There are many differential diagnoses that can cause focal neurologic symptoms in children and young adults, as shown in Table 1.

The etiology also varies according to gender, age, and geographic localization.[9] The main causes of ischemic stroke in this subset of the population are represented by congenital cardiac diseases and sickle cell anemia.[17] However, up to 50% of pediatric patients do not present any etiological evidence.[18] The main risk factors found in patients with stroke in the child population are presented in Table 2. The prevalence of risk factors differ in the literature.[7,10]

The management of stroke in children and young adults can be divided into initial and general supportive measures, diagnostic modalities, and appropriate treatment to the type of stroke identified, if possible.[10]

General supportive measures include maintaining normal oxygenation, treating dehydration, correcting anemia, controlling systemic hypertension with mild

permissive high levels, normalizing serum glucose, and controlling fever.[10]

An imaging test must be done to exclude a hemorrhagic cause of stroke after the initial supportive measures. The non-contrast CT has great sensitivity to exclude any acute bleeding, and MRI can be useful for the early detection of an infarction. MR arteriography, CT angiography, or catheter angiography are used to study the vascular anatomy and to confirm vessel patency.[10] Other investigations that may be useful are an ECG, a chest radiograph, and transthoracic or transesophageal echocardiography.[10]

There are no guidelines that establish the laboratory tests that should be assessed in the children and young adult population,[10] but it makes sense for the tests to include those that can help the differential diagnosis (Table 1) and to find the possible risk factors (Table 2).

In our case, a thorough diagnostic work-up focused on the risk factors that were potentially associated with cerebral ischemic events, and migraine was the unique detected risk factor. The presence of the positive ANA in the absence of detectable autoantibodies and

Table 1. Differential diagnosis of arterial ischemic stroke in children[8,10-16]

Venous occlusion of cerebral veins or sinuses
Hemorrhagic stroke
Complicated migraine
Transient postictal focal neurologic symptoms (Todd's paresis)
Intracranial neoplasm
Intracranial infections (meningitis, brain abscess, herpes simplex encephalitis)
Metabolic disorders (hypoglycemia, MELAS) • Hypoglycemia • MELAS
Traumatic hematomas (extradural, subdural)
Demyelinating conditions

MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like symptoms.

Table 2. Risk factors of stroke in childhood[7,10,13]

Cardiac disorders (congenital heart disease, patent foramen ovale, after cardiac surgery [immediate or not] and catheterization, acquired heart disease [rheumatic heart disease, cardiomyopathies, endocarditis, prosthetic valves])
Hematologic disorders (sickle cell disease, prothrombotic states [acquired thrombophilia, genetic thrombophilia], iron deficiency, hematological malignancy)
Infection (varicella, HIV, meningitis/encephalitis, pharyngitis, otitis media, sinusitis, matoiditis, sepsis)
Vascular disorders (arteriovenous malformations, moyamoya, arterial dissection, vasculitis)
Syndromic and metabolic disorders (Marfan syndrome, homocysteinuria, nutritional deficiencies [folic acid, vitamin B12], Down syndrome) **Connective tissue disease** **Extracranial solid tumors** **Acidosis, anoxia, dehydration, shock**
Trauma
Drugs (oral contraceptive, amphetamines, ecstasy, cocaine, phencyclidine, glue sniffing, ergot alkaloids)
Migraine **Ventriculoperitoneal shunt** **PHACES syndrome** **Risk factors for atherosclerosis in adulthood** (hypertension, hyperlipidemia, type 1 diabetes mellitus)

PHACES = malformations of the posterior fossa, facial hemangioma, arterial cerebrovascular anomalies, cardio-vascular anomalies, abnormalities of the eye and sternum.

normal complement was interpreted as with feeble correlation with any autoimmunity disorder; therefore the positive ANA could be explained by the acute event.[19]

Migraine is a chronic neurovascular entity, which is present in 11% of the general population (men and women) of all ages. In the female population of all ages, migraine is present in 17%; however, this increases to 23.5% between the ages of 18 and 44 years old.[20,21]

Migraine is an independent risk factor for cardiovascular diseases. Patients with the diagnosis of migraine have a 1.5 times greater risk of developing acute myocardial infarction, angina, and stroke,[22] which increases mortality by cardiovascular diseases by 1.37 times.[23] The main risk is related to cerebral ischemia.[24,25]

The diagnostic work-up of a focal deficit in a young woman should always consider the migraine as a potential risk factor or the etiology of the ischemic event, since in this subset of the population the etiology of stroke is determined in only 40% of cases.[26]

A stroke in a person with migraine should be differentiated into: (i) the cerebral infarction of other cause in a person that has migraine (cerebral ischemia associated with migraine); (ii) the cerebral infarction of other cause presenting with symptoms resembling migraine with aura; and (iii) the migrainous infarction. They present diverse physiopathological mechanisms, and the therapeutic approach should be different.[27]

Cerebral ischemia associated with migraine represents every cerebral ischemic event in patients diagnosed with migraine. The patient who has a stroke during a migraine crisis with neurological focal signs that are different from the previous aura could be diagnosed with a cerebral infarction of other cause presenting with symptoms resembling migraine with aura.[27]

Migraine is a risk factor associated with cerebral ischemia mainly in women under the age of 45 years who use an oral contraceptive and smoke tobacco (independent risk factors). Migraine with aura presents the relative risk of 2.16 (confidence interval 95%, 1.53-3.03), although there are controversies in the literature.[24,28,29] The presence of migraine in children with ischemic stroke in the study of Mackay et al.[9] was 3%. The frequency of migraine attacks also affects the risk of ischemic stroke; that is, the greater the number of attacks, the greater the risk.

In addition to being the cause of a stroke, migraine enhances the risk of CNS ischemia by different mechanisms. There are many hypotheses to explain the association of migraine and stroke, which include (i) the adverse effect of migraine-specific medication;[30] (ii) genetic associations that cause a predisposition to the hyperactivity of vessels; (iii) endothelial dysfunction that causes a predisposition to atheromatous plaque formation and its instability associated with procoagulant, proliferative, and proinflammatory states; and (iv) the prevalence of some conditions, such as arterial dissection; the presence of a patent foramen ovale; and clotting disorders, such as thrombophilia.[31] Migraine also increases the risk of hemorrhagic stroke by still unknown causes.[32]

According to the third edition (2013) of the International Classification of Headache Disorders,[27] migrainous infarction is defined as: "One or more migraine aura symptoms associated with an ischaemic brain lesion in the appropriate territory demonstrated by neuroimaging" (p. 651). Also, as diagnostic criteria, the aura must be typical of previous attacks, the focal deficit must remain longer than 60 minutes and it must be associated with the pain crisis, which fulfils the criteria of a migraine attack not explained by any other cause. The incidence of migrainous infarction is low, accounting for 0.2-0.5% of all cerebral ischemic causes.[33,34] The physiopathology is still uncertain; however, the main hypothesis relates to an imbalance in the vessels' control with severe vasoconstriction followed by downstream ischemia.[30] The territory of the posterior circulation is mostly involved (70-82%). Young women are more affected, probably with a bias of selection, since the migraine with aura by itself is more frequent in this population.[31] The imaging examinations more often reveal single or multiple small lesions limited to an unique vascular territory.[35] The prognosis is generally favorable with complete recovery of the neurological deficits.[36] Our patient could not meet the criteria for migrainous infarction, because the presented symptoms were not part of the crises previously presented.

The management of migraine in patients with ischemic stroke involves the avoidance of some drugs that can induce migraine in those patients, such as cilostazol[37] and dipyridamole,[38] and prescribing a treatment for preventing migraine.[30] A beta-adrenergic

blocker and a calcium channel blocker are well established for this propose.[39,40] Statins, angiotensin receptor blockers, and angiotensin-converting-enzyme inhibitors have been reported as effective for migraine prophylaxis.[41-43]

The pharmacological prevention of stroke in migraineurs is not well established.[30] It is important to eliminate modifiable risk factors, such as smoking and the use of oral contraceptives. Antihypertensives and statins must be used according to the indications. There are no recommendations for the use of antithrombotics to reduce the risk of stroke in this population.[30]

By definition and by exclusion, after extensive diagnostic investigation, we arrived at the diagnosis of cerebral infarction of other cause presenting with symptoms resembling migraine with aura, since the patient presented a typical episode of migraine with visual aura, and developed focal neurological signs that were different from those presented in previous auras, which made it impossible to fulfill all the criteria for migrainous infarction, excluding the main causes investigated for a cerebral infarction.

CONCLUSION

The case presented herein illustrates the case of a midbrain ischemic stroke in a young female, which was confirmed by the medical history, the neurological examination, the imaging examinations, and the extensive work-up, which ruled out a wide range of other possible etiologies. Although migrainous infarction is not common in medical practice, it is important to be reminded of its etiological role in young patients with headache and a lasting focal deficit.

Patients with migraine should be advised to prevent the modifiable risks factors, such as tobacco smoking, oral contraceptive use, obesity, a sedentary lifestyle, and treat—when indicated—the chronic migraine and other comorbidities, such as diabetes, hypertension, and dyslipidemia, to decrease the likelihood of ischemic episodes.

ACKNOWLEDGMENTS

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