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**BIBLIOGRAPHIC REVIEW**

# Approach to the diagnosis of ischemic cerebral infarction in young adults

## Aproximación al diagnóstico infarto cerebral isquémico en adultos jóvenes

## Abordagem para o diagnóstico de infarto cerebral isquêmico em adultos jovens

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## ABSTRACT

**Introduction:** ischemic stroke in young adults has emerged as a relevant health problem today due to its increased incidence, high mortality, the duration of the disability and social consequences. **Objective:** to describe an approach in diagnosis of ischemic stroke in young adults based on etiopathogenic classification, history and complementary investigations. **Method:** a wide-ranging bibliographic review was carried out using Google Scholar, searching in bibliographic databases like PubMed, SciELO and Medline, and searching different keywords; 32 articles were chosen in the process with title and abstract were linked with the subject of this review. **Development:** the etiopathogenic subtypes of ischemic stroke in young adults differ with regard to older adults, and its etiologic causes are more diverse and heterogeneous. Risk factors, personal and family pathological history, non-neurological and neurological clinical manifestations, allow an approach to diagnosis, while complementary investigations facilitate the confirmation of diagnosis, the location and size of the ischemic infarction, definition of the etiological cause and the support of therapeutic decisions. **Final considerations:** the history and clinical manifestations obtained through interrogation and physical examination, in association with complementary investigations, made it possible an approach to diagnosis of etiopathogenic subtype and the cause of ischemic brain infarction in young adults improving treatment possibilities.

**Keywords:** ischemic stroke in young adults; diagnostic approach; clinical manifestations; complementary investigations

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## RESUMEN

**Introducción:** el infarto cerebral isquémico (ICI) en adultos jóvenes ha emergido como un relevante problema de salud debido al incremento de su incidencia, alta mortalidad, larga duración del tiempo de la discapacidad y consecuencias sociales. **Objetivo:** describir una aproximación al diagnóstico del infarto cerebral isquémico en adultos jóvenes sobre la base de la clasificación etiopatogénica, historia e investigaciones complementarias. **Método:** se realizó una extensa revisión bibliográfica con el buscador Google Académico, en las bases de datos bibliográficas PubMed, SciELO y Medline, y con la búsqueda de palabras claves; siendo escogidos 32 artículos cuyo título y resumen se relacionaron con el tema de la presente revisión. **Desarrollo:** los subtipos etiopatogénicos del infarto cerebral isquémico en adultos jóvenes difieren al compararlo con adultos mayores, y sus causas etiológicas son más variadas y heterogéneas. Los factores de riesgo, antecedentes patológicos personales y familiares, manifestaciones clínicas no neurológicas y neurológicas, permiten un acercamiento al diagnóstico, mientras que las investigaciones complementarias facilitan la confirmación del diagnóstico, la localización y tamaño del infarto isquémico, el establecimiento de la causa etiológica y el sustento de las decisiones terapéuticas. **Consideraciones finales**: la historia y manifestaciones clínicas obtenidas mediante el interrogatorio y examen físico, unido a las investigaciones complementarias, posibilita la aproximación al diagnóstico del subtipo etiopatogénico y a la causa del infarto cerebral isquémico en adultos jóvenes, lo que mejora las posibilidades de tratamiento del mismo.

**Palabras clave:** infarto cerebral isquémico en adultos jóvenes, aproximación al diagnóstico, manifestaciones clínicas, investigaciones complementarias

## RESUMO

**Introdução:** oacidente vascular cerebral (AVC)isquêmico em adultos jovens emergiu como um problema de saúde relevante devido à sua crescente incidência, elevada mortalidade, longa duração da incapacidade e consequências sociais**Objetivo:** descrever uma abordagem ao diagnóstico do AVC isquêmico em adultos jovens baseada na classificação etiopatogénica, na história e em exames complementares. **Método:** foi realizado uma extensa revisão bibliográfica utilizando o motor de busca Google Scholar, as bases de dados bibliográficas PubMed, SciELO e Medline, e uma pesquisa por palavras-chave; foram selecionados 32 artigos cujo título e resumo estavam relacionados com o tema desta revisão. **Desenvolvimento:** os subtipos etiopatogênicos do AVC isquêmico em adultos jovens diferem quando comparados aos adultos mais velhos, e suas causas etiológicas são mais variadas e heterogêneas. Os fatores de risco, os antecedentes patológicos pessoais e familiares, as manifestações clínicas não neurológicas e neurológicas permitem uma aproximação ao diagnóstico, enquanto as investigações complementares facilitam a confirmação do diagnóstico, a localização e o tamanho do infarto isquêmico, o estabelecimento da causa etiológica e o apoio às decisões terapêuticas. **Considerações finais:**a história e as manifestações clínicas obtidas por meio de questionamento e exame físico, juntamente com investigações complementares, permitem abordar o diagnóstico do subtipo etiopatogênico e a causa do AVC isquêmico em adultos jovens, melhorando as possibilidades de seu tratamento.

**Palavras-chave:**acidente vascular cerebralisquêmico em adultos jovens, abordagem diagnóstica, manifestações clínicas, investigações complementares

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## INTRODUCTION

Ischemic Cerebral Infarction (ICI) accounts for 87% of all Cerebrovascular Accidents (CVA).[1] Most ICIs occur in older adults.[2] The prevalence of ICI in young adults shown by various studies[2,3] is between 10 and 15%. Evidence from several studies conducted in recent years points to an increase in ICI in young people;[4,5] in contrast, ICI in adults over 65 years of age has decreased.[6]

Although there is no standard criterion to establish the upper age limit, most researchers consider between 50 and 55 years to define ICI in young adults.[5,7]

ICI in young adults has emerged as a relevant health problem as a result of increased incidence, high mortality, long duration of disability and social consequences.[4,6,8,9] Young adults with ICI who survive the acute event often have cognitive impairment, depression, and epilepsy[7,8] that impair quality of life, many needing a caregiver.[8]

Recent advances in the field of neuroimaging, identification of cardiac structural defects by ultrasound, the development of new methods of genetic studies, personalized and therapeutic prevention of ICI, genetic cause, pharmacological management of the specific cause, revascularization procedures, have improved the possibilities for diagnosis and treatment of ICI in young adults.[10,11,12]

Therefore, it was decided to conduct an investigation with the aim of describing an approach to the diagnosis of ischemic cerebral infarction in young adults based on etiopathogenic classification, history and complementary investigations.

## METHOD

The search and analysis of the information was performed over a period of 62 days (December 1, 2022 to January 31, 2023) and the following words were used: *ischemic stroke in young adults, approach to diagnosis; ischemic stroke in young adults and approach to diagnosis,* clinical manifestations and complementary investigations. The Boolean operators OR or AND were used to direct the search as appropriate.

Based on the information obtained, a bibliographic review of a total of 81 articles published in the PubMed, SciELO and Medline databases was carried out using the Google Scholar search engine; of these, 32 selected citations were used to carry out the review; 26 from the last five years.

Review studies, original studies and management guidelines were used. Research that did not offer information of value for the review was excluded.

## DEVELOPMENT

### Etiopathogenic classification

The etiopathogenic classification of ICI facilitates the approach to diagnosis and therapeutic management of patients. One of the most widely used is TOAST (Trial Org-10172 Acute Stroke Treatment).[13,14]

TOAST classification of etiopathogenic subtypes of ICI:
- Large artery atherosclerosis (thrombosis/embolism).
- Cardioembolic ischemic cerebral infarction (high risk/medium risk).
- Small vessel occlusion (lacunar infarction).
- Ischemic cerebral infarction of determined cause.
- Ischemic cerebral infarction of undetermined cause (cryptogenic infarction).

- ≥ 2 identified causes.
- Negative assessment.
- Incomplete evaluation.

The frequency of presentation of the etiopathogenic subtypes of ICI in young adults is different from that in older adults. Cardioembolic infarction, myocardial infarction of undetermined cause, and myocardial infarction of undetermined cause predominate in young adults, whereas atherosclerosis of large arteries and occlusion of small vessels predominate in older adults.[2,15,16]The risk factors and etiologic causes of ICI in young adults are multiple and heterogeneous.

### Causes of ischemic cerebral infarction in young people

I- Cardioembolic infarction
II- Atherosclerotic vascular lesion large intra and extracranial arteries
III- Small vessel disease: vascular lesion caused by lipohyalinosis, arterial hypertension

IV- Non-atherosclerotic vasculopathies
- Hereditary: CADASIL, CARASIL, Fabry disease, MELAS.
- Dissection of intra and extracranial arteries.
- Fibromuscular dysplasia.
- Moyamoya disease.
- Reversible Cerebral Vasoconstriction Syndrome (RCVS).

V- Inflammatory vasculopathies.

- Primary vasculitis:

Primary vasculitides of the central nervous system

Systemic vasculitis:

- Vasculitis caused by collagen diseases: SLE.
- Vasculitis caused by infections: syphilis, AIDS.

VI- Hematological conditions (prothrombotic states).

- Hereditary: factor V Leiden mutations, prothrombin gene G20210A mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, homocystinuria, sickle cell anemia.
- Acquired: antiphospholipid syndrome, myeloproliferative disorders, pregnancy and puerperium, oral contraceptives, cancer, use of anabolic steroids.

VII- Other determined causes

- Use of illicit drugs: cocaine, heroin, amphetamines.
- Migraine.

VIII- Infarction of undetermined cause or cryptogenic

**Approach to the diagnosis of ICI in young adults**

a) Risk factors. ICI in young adults has a greater diversity of risk factors and possible causes than in older adults.[9] These include:

- Vascular risk factors. The presence and impact of vascular risk factors in young adults has increased.[9,16] Epidemiological research confirms the association of vascular risk factors and the occurrence of ICI in young adults.[17] Hypertension, diabetes mellitus, dyslipidemia, and obesity are among the vascular risk factors most frequently associated with ICI in young adults.[16,18]

- Lifestyle-associated risk factors. Lifestyle-related risk factors including smoking, high alcohol consumption, illicit drug abuse (cocaine, heroin, amphetamines), and lack of physical activity, which are more frequently present in young adults, increase the risk of ICI.[15]

- Risk factors only present in young people. There are risk factors for ICI present only in young people, such as:
  - Pregnancy and puerperium: Pregnancy is a recognized risk factor for ICI, however, it rarely occurs. A review and meta-analysis found that ICI occurs in less than 20 per 100,000 pregnancies.[19]The puerperium is a proven risk factor for ICI.[20] Several pathophysiological alterations and conditions associated with pregnancy, including hypercoagulable state, eclampsia, amniotic fluid embolism, peripartum cardiomyopathy, and CRPS are associated with ICI.[21]

- Oral contraceptive use: studies conducted in the 1970s linked increased ischemic ICI to the use of oral contraceptives with high estrogens content.[22] Research has found no evidence that oral contraceptives with low estrogens doses (≤ 50 mcg estrogens) increase the risk of ICI.[22] The concurrence of other risk factors for vascular damage (hypertension, smoking, diabetes mellitus) in users of oral contraceptives increases the likelihood of ICI.[22]

b) Personal Pathological Antecedents (PPA): it is important to specify in the PPA related to the occurrence of ICI, among them:

- Cardiac diseases: cardioembolic ICI is of frequent presentation in young adults,[10] 18.7%.[15] Dilated cardiomyopathy, intracardiac thrombus, atrial myxoma (conditions of high cardioembolic risk), persistent foramen ovale, atrial septal defect, and non-bacterial thrombotic endocarditis (conditions of medium cardioembolic risk) are more frequent in young adults than in older adults, while non-valvular atrial fibrillation predominates in older adults.[15]
- Migraine: research supports the association between migraine and ICI, particularly migraine with aura in women under 45 years of age, while this relationship is uncertain in migraine without aura and in men.[25]
- Cancer: cancer is a risk factor for ICI in young adults.[26] Consequences of the cancer itself and from the effects of treatment such as direct effects of a solid tumor, hypercoagulation, accelerated atherosclerosis, chemotherapy action and long-term vascular damage from radiotherapy explain the relationship between cancer and ICI.
- Infections: there is a complex relationship between ICI and infections. Both acute and chronic infections through various pathophysiological mechanisms can directly cause or be a risk factor for ICI.[7] Among these pathophysiological mechanisms are:

  - Vascular wall damage by direct invasion, vasculitis of small and large vessels, endotheliopathy.
  - Triggering of cerebral infarction (promotion of a hypercoagulable state, platelet activation, dehydration, infection-induced cardiac arrhythmias)
  - Acceleration of atherosclerosis through induction of cytokines (TNF alpha, interleukin 2) in response to specific antigenic stimuli.
  - Chronic inflammation due to multiple infections.[4,27] Multiple bacterial (meningoencephalitis, syphilis, tuberculosis, periodontal disease, Helicobacter pylori infestation), viral (HIV, herpes simplex virus, cytomegalovirus), parasitic (Chagas disease, neurocysticercosis) and fungal (cryptococcal infection, aspergilliosis, mucormycosis) infectious conditions are implicated in the occurrence of ICI. Syphilis, HIV, tuberculosis, neurocysticercosis, and Chagas disease should be suspected in young patients with ICI in endemic areas or with risk factors for these infectious diseases.

c) Family Pathological Antecedents (FPA): hereditary conditions with different mechanisms of hereditary transmission (autosomal dominant, autosomal recessive, X-linked, maternal) are associated with the occurrence of ICI early in life. Among them:

- Hereditary thrombophilias: factor V Leiden mutations, prothrombin gene G20210A mutation, protein C deficiency, protein S deficiency and antithrombin III deficiency homocystinuria. A history of venous thromboembolism in two or more first-degree relatives raises suspicion of hereditary thrombophilia.
- Monogenic conditions: dominant autonomic cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), recessive autonomic cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), Fabry disease and mitochondrial myopathy with encephalopathy, acidosis and stroke-like episodes (MELAS).

**Clinical manifestations**

Given the heterogeneous nature of the causes of ICI in young people, it is important in the approach to diagnosis to determine the clinical manifestations that lead to suspect a specific condition. Among these:

a) Non-neurological manifestations.

- General manifestations: asthenia, anorexia, and weight loss lead to the suspicion of cancer as a risk factor for ICI in a young adult. Symptoms and signs of systemic inflammation such as fever, night sweats, asthenia, anorexia, weight loss, arthralgias and arthritis support the suspicion of systemic vasculitis.
- Cardiovascular manifestations: dyspnea, palpitations, anginal pain, syncope may be an expression of valvular disease, cardiac arrhythmias or acute myocardial infarction in a patient with cardioembolic ICI. These same symptoms appear as an expression of cardiac damage in Fabry disease. Physical examination may reveal the presence of murmurs and arrhythmic heartbeats on auscultation. In fibromuscular dysplasia, renovascular hypertension may cause ICI.
- Venous thromboembolic events: the absence of predisposing factors, occurrence of the first event of venous thromboembolism without a defined cause in patients under 50 years of age, recurrent episodes of idiopathic venous thromboembolism and localization in unusual vascular territories allow the suspicion of hereditary thrombophilia. In a woman of childbearing age with a personal history of spontaneous abortions and recurrent venous thromboembolism, the diagnosis of antiphospholipid syndrome should be considered.
- Renal manifestations: albuminuria, hematuria and reduced estimated glomerular filtration rate (eGFR) in systemic vasculitis, collagen diseases and Fabry disease.
- Dermatological manifestations: in primary central nervous system vasculitis a cutaneous rash may appear, while in primary systemic vasculitis palpable purpura, urticaria, ulcers, livedo reticularis and nodules are found. One of the characteristic manifestations of Fabry disease is angiokeratoma. Butterfly wing erythema and discoid erythema are seen in patients with systemic lupus erythematosus.

- Osteomioarticular manifestations: homocystinuria presents bone manifestations, the most frequent being osteoporosis, elongation of the long bones, anomalies in size and shape of the epiphyses, wide or spiculated metaphyses, biconcave vertebrae, pes cavus and arched palate. Vaso-occlusive crises of sickle cell disease characterized by bone pain can cause ICI. A myopathy is one of the manifestations of MELAS syndrome. Collagen diseases present with arthralgias and joint inflammation.
- Cervical and facial pains are prominent symptoms in extra- and intracranial arterial dissection. Neuropathic pain (perceived as burning, tingling or hypersensitivity to friction or cold) is part of the clinical manifestations of Fabry disease.

b) Neurological manifestations

- Headache: it is a relevant symptom in some of the conditions that originate an infarction of determined or unusual cause. The clinical characteristics of the headache can orient the possible origin. Migraine with aura is an ICI risk factor in young adults; it is part of the clinical manifestations of hereditary conditions such as CADASIL and MELAS. Reversible cerebral vasoconstriction syndrome presents among its relevant symptoms an acute onset headache of great intensity; a thunderclap headache. It is a relevant symptom in intracranial and extracranial artery dissection, as well as in Primary Vasculitis of the Central Nervous System (PCNSV).
- Seizures: in the initial phase of cardioembolic cerebral infarction, seizures frequently appear. They are part of the symptomatic course of both primary central nervous system vasculitis and systemic vasculitis and may appear in the disease.
- Dementia: Cognitive impairment with early-onset dementia is a clinical feature of inherited CADASIL, CARASIL and MELAS conditions. Progressive cognitive impairment may occur in NPSV.
- Mental retardation is one of the manifestations of neurological damage in homocystinuria.
- Hereditary and acquired prothrombotic states cause cerebral venous thrombosis, the clinical manifestations of which are expressed by: headache, focal neurological deficit, seizures and encephalopathy.[28]

**Complementary investigations**

a) Imaging studies

There is no universal imaging study algorithm for young adults with ICI.[10] Imaging studies, computed tomography (CT) and magnetic resonance imaging (MRI) allow: a) confirm the diagnosis of ICI, its size and location, whether it is single or multiple, b) exclude the diagnosis of intracerebral hemorrhage (ICH) or confirm its presence accompanied by ICI, c) establish the differential diagnosis with entities that simulate ICI and d) show findings that contribute to the diagnosis of specific causes of ICI in young adults.

In the emergency department the first study to be performed is CT mainly because it allows a quick evaluation and selection of appropriate patients for thrombolysis with Plasminogen Activating Factor (tPA).[10,12]

MRI has an important role in the diagnostic evaluation of young adults with ICI. MR images have a higher sensitivity and spatial resolution when compared to those obtained by CT, being superior for establishing the ischemic origin, extension and location of the lesion and allowing the identification of specific causes of ICI.[10]

b) Angiographic studies.

They allow demonstrating atherosclerosis of large intra- and extracranial arteries and identifying images of non-atherosclerotic vasculopathies.

Tomography angiography (CTA) and resonance angiography (MRA) are part of the imaging evaluation in young adults with ICI, they are superior to conventional angiography (CA) in demonstrating dissection of the vascular wall of the large neck arteries.[10] CA is adequate for the evaluation of stenotic or occlusive lesions of large intracranial arteries, it is indicated prior to the revascularization of intra and extracranial arteries.[8]

c) Ultrasonographic studies.

- Carotid and transcranial Doppler ultrasound for the study of large extra and intracranial arteries.
- Transthoracic echocardiography (TTE) is the initial study in a patient with cardioembolic infarction; if the cause cannot be established, transesophageal echocardiography (TEE) is indicated.
- Molecular techniques for the study of hereditary thrombophilias are not part of the initial evaluation; they are only indicated when there is clinical suspicion. These include: DNA analysis for the prothrombin gene, DNA analysis for Factor V Leiden, functional chromogenic test complemented with immunoassay (ELISA) for protein C and S deficiency.
- Genetic study for the diagnosis of hereditary non-atherosclerotic vasculopathies.[11]

**Approach to diagnosis according to ischemic stroke subtype**

*Atherosclerosis of large arteries:* Although atherosclerosis of large arteries related to ICI is frequent in the elderly, it is infrequent in young adults, representing only 2% to 8% of ICI in young adults.[15]

The diagnosis of atherosclerosis of large arteries is suspected in the presence of risk factors for atherosclerotic damage and evidence of atherosclerosis in other organs (ischemic heart disease, aortic disease, peripheral artery disease). In the interrogation a history of transient ischemic attack can be collected and in the examination a carotid bruit on the brain lesion side.

The clinical manifestations found in ICI caused by atherosclerosis of large arteries depend on whether it affects the territory irrigated by the anterior circulation or the territory irrigated by the posterior circulation, and according to the Oxford shire or Bamford classification[29] in:

- Total anterior circulation syndrome includes:

- Unilateral motor, sensory or both deficits affecting at least two of face, arm and leg.
- Upper cerebral dysfunction.
- Homonymous hemianopsia.

- Partial anterior circulation syndrome: two of the three components of total anterior circulation syndrome or pure superior cortical dysfunction, pure motor or sensory deficit, but not as extensive as in a lacunar syndrome.

Cerebral dysfunction is expressed by aphasia (motor, sensory or both), constructional apraxia (difficulty in drawing complex two- or three-dimensional figures), neglect, dyscalculia, dysarthria without aphasia may occur. In the presence of altered consciousness, cerebral dysfunction is assumed.

- Posterior circulation syndrome:
- Isolated hemianopsia.
- Signs of brain stem.
- Cerebellar ataxia (inability to coordinate balance, gait, limb and eye movements).

The existence of a hemiplegia or alternating hemiparesis (cranial nerve harvesting on the side of the lesion with harvesting of the contralateral hemibody) defines that the lesion is at the brainstem level.

The diagnosis of large artery atherosclerosis is corroborated by demonstrating stenosis > 50% of the arterial lumen, occlusion or ulcerated plaque (>2 mm deep) of the intracranial or extracranial artery on US Doppler, conventional angiography, CTA or MRA. CT/MRI shows ischemic infarction >1.5 cm cortical or subcortical, in carotid or vertebrobasilar territory.

*Cardioembolic infarction:* In young adults it is the most frequent subtype.[15] It is characterized by the acute onset of focal neurological deficit in seconds or a few minutes of wakefulness, often with seizures at the beginning of the picture, the loss of consciousness may be transient. A history of transient ischemic attacks or cerebral infarcts in several vascular territories can be collected and systemic embolisms can coexist and occur in different locations at the same time.

For the diagnosis of PPA it is necessary to establish the presence of an emboligenic condition, murmur and/or arrhythmia in cardiac auscultation, electrocardiographic identification of a cardiac arrhythmia, and demonstration of cardiac structural lesion by TTE or TEE), presence in CT of cerebral infarction >1.5 cm usually located in the cerebral cortex or there may be multiple infarctions in different vascular territories.

Small vessel disease (lacunar infarction): It is more frequent in older adults than in young adults, representing between 7% to 14% of ICI in young adults.[2,13] Small vessel disease is caused by occlusion of the cerebral microcirculation, due to lipohyalinosis or microatheromatosis.[30]

Its clinical manifestations depend on the location of the occluded vessel and are expressed by:

- Pure motor hemiparesis.
    - Unilateral motor deficit affecting face, arm and leg without objective sensory manifestations. Motor seizure may not be total, involving face and arm or arm and leg. It does not include the seizure of a single limb.

- Pure sensory syndrome.
    - Unilateral sensory deficit involving face, arm and leg. Paresthetic sensations and/or unilateral hyperesthesia.

- Ataxic hemiparesis.

    - Hemiparesis of crural predominance and ataxia of the same side of the motor deficit. May be accompanied by sensory symptoms or deficits.

- Dysarthria clumsy hand.
    - Dysarthria with facial weakness and clumsiness of the hand.

- Sensory motor syndrome.
    - Ipsilateral sensory motor deficit of similar distribution to pure motor hemiparesis and pure sensory syndrome.

The diagnosis is confirmed by CT demonstration of an infarct of <1.5 cm.

The existence of manifestations of cortical involvement such as altered level of consciousness, seizures, aphasia, neglect, and oculomotor and visual disturbances exclude the diagnosis of small vessel disease.

Cerebral infarction of specific cause groups cerebral infarctions originating from specific conditions such as non-atherosclerotic vasculopathy, vasculitis, thrombophilias and hypercoagulable states and other causes.

The diagnosis of a given cause is suspected in the presence of a family history of hereditary thrombophilias and monogenic conditions, APP, non-neurological (general, cardiovascular, renal, dermatological, osteomioarticular) and neurological symptoms and signs suggestive of a specific cause of cerebral infarction. Thus we see that the presence of multisystemic manifestations suggests the diagnosis of a collagen disease, a current or preceding thromboembolic event or a thrombophilia. Complementary investigations allow the diagnosis of the different specific causes of cerebral infarction to be established.

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**Findings that allow to suspect and establish the diagnosis causes certain cerebral infarction**

Causes and findings
*Non-atherosclerotic vasculopathies*

- Hereditary: AD inheritance, NOTCH3 gene.

- CADASIL - Recurrent cerebral infarcts, migraine headache with aura, early-onset dementia, psychiatric manifestations.
  Image: MRI subcortical and periventricular white matter hyperintense lesions on T2-weighted images and Fluid-Attenuated Inversion Recovery (FLAIR). CT subcortical infarcts
  Genetic study, skin biopsy

- CARASIL - AR inheritance, HtrA serine peptidase 1 (HTRA1) protease activity or protein loss.
  Recurrent cerebral infarcts, premature dementia, premature baldness
  Genetic study

- Fabry disease - X-linked inheritance, α galactosidase A deficiency, males more severe phenotypes, angiokeratomas, cardiovascular manifestations (dyspnea, palpitations, syncope or angina), renal involvement (progressive renal disease with albuminuria, hematuria and reduced eGFR), neurological manifestations (recurrent cerebral infarcts, neuropathic pain, variable degree of cognitive impairment and psychiatric symptoms, vestibular and cochlear disorders).
  Image: MRI hyperintense images of white matter. CT subcortical infarcts
  Determination of α-galactosidase A activity.

- MELAS - Maternal inheritance, mitochondrial DNA variant (mtDNA).

  Lactic acidosis, myopathy, migraine headache, seizures, hearing loss, diabetes, acute focal neurological deficit not corresponding to a defined vascular territory
  Imaging: multifocal hyperintense cortico-subcortical lesions on FLAIR and diffusion-weighted images. CT cortico-subcortical infarcts, Both MRI and CT lesions do not correspond to a vascular territory.
  Lactic acid determination in blood and cerebrospinal fluid (CSF), torn red fibers in muscle biopsy
  Genetic study

- Intracranial and extracranial artery dissection: history of trauma, headache, facial pain, cervical pain, Horner's syndrome and cranial nerve palsies, in vertebral artery dissection signs of ischemia posterior circulation, subarachnoid hemorrhage.
  Imaging: CTA, MRA, CA (intramural hematoma, double lumen, stenosis, occlusion or aneurysm). CT/MRI ischemic infarction, subarachnoid hemorrhage (SAH). T1-weighted fat-saturated fat-weighted MRI is the most sensitive modality to show cervical arterial dissection.

- Fibromuscular dysplasia: more frequent in women, may be asymptomatic, cerebral infarction, renovascular AHT when it affects renal artery, aneurysm.
Image: AC, CTA, MRA (coin stack image produced by stenosis and dilatations).
US Doppler supra-aortic and transcranial trunks

- Moyamoya disease: early onset cerebral infarction, seizures.
Image: angiography shows stenosis or occlusion of the terminal portion of the internal carotid artery (ICA) and proximal portions of the anterior cerebral artery (ACA) or middle cerebral artery (MCA), vascular network in the vicinity of the occluded arteries and bilateral involvement.
- SVCR: related to precipitating factors (vasoactive substances, illicit drugs, migraine, puerperium, and eclampsia). Acute severe thunderclap headache, fluctuating focal neurological deficit, non-aneurysmal SAH
Imaging: AC is the standard reference for diagnosis vasoconstriction; CTA and MRA are employed initial evaluation. Multifocal imaging of large intracranial vessels is diagnostic of vasoconstriction but not specific for CRPS.

*Inflammatory vasculopathies*

- NPSV: headache, cognitive impairment, seizures, multifocal ischemic and/or hemorrhagic lesions in various stages; no signs of systemic disease.
Imaging: intense focal concentric vascular wall enhancement in IPV finding indicating inflammation.(45) MRI multiple infarcts in different territories. MRA/CA focal or multifocal segmental narrowing of small and medium intracranial arteries
CSF study: pleocytosis, proteinorraquia; brain biopsy.

- Primary systemic vasculitis: malaise, fever, weight loss, rash, neurological symptoms as in NPSV, organ involvement depending on the disease.
Imaging: findings similar to NPSV.
Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein and specific antibodies: anti-cytoplasmic neutrophil-perinuclear antibodies, myeloperoxidase, anti-neutrophil cytoplasmic antibodies, proteinase CSF study (pleocytosis, proteinuria).

- Vasculitis secondary to collagenous diseases: multiple organ and system involvement.
Complete blood count
Specific antibodies: antinuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-dsDNA).
- Infectious vasculitis: APP, risk factors.
Serological studies
Hematologic conditions

- Hereditary thrombophilias: APF of VTE in two or more first-degree relatives, recurrent VTE episodes with defined cause, first idiopathic VTE episode at < 50 years of age.
Focal neurological deficits, seizures, isolated endocranial hypertension.
Image: CT a) cord sign elongated hyperdense elongated image in cortical vein thrombosis, b) dense triangle sign hyperdensity at superior sagittal sinus level, c) empty delta sign in contrast CT full defect surrounded by contrasting venous sinuses. Computed tomography venography (CTV) shows the filling defect, venous wall reinforcement and increased contralateral venous drainage. MRI directly visualizes the thrombus,[31] up to 5 days isointense T1 and hypointense in T2/FLAIR, from 6 to 15 days hyperintense T1, T2 and FLAIR, from 16 days T1, T2 and FLAIR isointense T2 and FLAIR can remain hyperintense.
Coagulation study: prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen.

Molecular techniques for the study of thrombophilias
- Homocystinuria: AR inheritance, cystatoninβ-synthetase deficiency.
Arterial and venous thromboembolic events, mental retardation, seizures, neuropsychiatric disorders, extrapyramidal symptoms, bone and ocular manifestations

Elevated homocysteine and methionine levels

- Antiphospholipid syndrome: recurrent venous and/or arterial thrombosis, spontaneous abortions, eclampsia, lupus anticoagulant, anticardiolipin antibodies, anti-2-glycoprotein antibodies.

*Other causes*

- Illicit drugs: history of drug abuse, intravenous injection marks.
Toxic determination in urine, blood and gastric contents

- Migraine infarction: APP migraine with aura, cerebral infarction associated with typical aura.
The diagnosis of migraine with aura according to International Headache Society criteria,[32] there are no specific diagnostic tests.

Cerebral infarction of undetermined cause: Ischemic infarction may be considered as undetermined cause after standard evaluation when the clinical examination and neuroimaging suggest a superficial infarction or large deep cerebral infarction, but none of the tests performed can diagnose a possible cause of ischemic cerebral infarction.[13]

## FINAL CONSIDERATIONS

The etiopathogenic subtypes of ischemic cerebral infarction in young adults differ when compared to older adults. In young adults, cardioembolic infarction predominates, both of determined and undetermined cause; whereas in older adults, atherosclerosis of large arteries and occlusion of small vessels predominate and their etiologic causes are more varied and heterogeneous. The history (risk factors, APP and APF) and the clinical manifestations obtained by interrogation and physical examination of the patient together with the rational use of complementary investigations make it possible to approach the diagnosis of the etiopathogenic subtype and cause of ischemic cerebral infarction in young adults, improving the possibilities of treatment.

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