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HEADACHES AND CEREBROVASCULAR DISEASE

Headache in cervicocerebral artery dissection

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Abstract
Cervicocerebral artery dissection (CAD) is one of the more frequent causes of stroke in young adults with rates of up to 25%. Predisposing and risk factors for CAD are very different, and an etiological classification is based on the presence of a previous minor or major trauma, differentiating traumatic from spontaneous CAD. Headache represents one of the main initial symptoms for this pathological condition, probably due to the release of pro-inflammatory neurotransmitters from nerve terminals near the injured vessel. For its peculiar characteristics, the headache due to CAD has been defined with specific ICHD-3 criteria. In many cases, headache is associated with other signs related to the dissection or cerebral ischemia. In this systematic review of literature, headache was reported in more than 70% of cases with CAD with a prevalence in vertebrobasilar dissections. More than half of patients suffered a severe pain that was usually located in fronto-temporal and occipito-nuchal regions in the case of dissections in the anterior and posterior circulation, respectively. For the high stroke risk, CAD has to be promptly diagnosed with MRI or CTA and treated with anticoagulants or antithrombotics.

Keywords Headache · Migraine · Cervical artery · Intracranial artery · Dissection

Introduction

Cervicocerebral artery dissection (CAD) is one of the leading causes of stroke in young adults [1–3]. Miller Fisher reported the first description of this pathological condition in the 1970s [4]. Dissections refer to a tear in the wall of an artery located in an extra- or intracranial site. CAD is classified based on artery involvement (carotid and vertebral) and the location of the involvement (intracranial or extracranial/cervical). It is considered as a cervical artery dissection when this injury occurs in the internal carotid or vertebral artery, outside the skull. When the primary dissection is located above the petrous bone, it is referred to as an intracranial dissection. Previous reports showed that about 2% of all ischemic stroke patients was affected by CAD, but this rate increases if young age is considered (up to 25%) [5]. In this population, the annual incidence rate is 2.6 to 2.9 per 100.000 [6]. However, the true incidence of this pathological condition may be higher because of an underdiagnosed CAD. Overall, in previous studies, the median age of occurrence is 45 years with a slight prevalence for males.

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Pathophysiology and risk factors for CAD

As previously reported, the arterial dissections are secondary to a tear in the layers of the arterial wall, mainly between media and intima. This condition is usually complicated by blood entering this wall, leading to a thrombus [3]. The CAD could be consequence of a major or minor trauma, including sport injuries or cervical manipulation. On the contrary, they are defined as spontaneous if no preceding trauma event is detected. While the first type of CAD is more common in extracranial arteries, spontaneous CAD can occur in extra- and intracranial arteries. Many risk and predisposing factors have been studied and identified. Three main categories should be considered: (1) genetic predisposition, (2) environmental triggers, and (3) risk factors. Genetic predisposition to CAD has been well documented in Ehler-Danlos vascular syndrome, Marfan's syndrome, fibromuscular dysplasia, osteogenesis imperfecta, cystic medial necrosis, and in autosomal dominant polycystic kidney disease [6]. Some evidences

reported also the MTHFR C677T mutation and the alfa-1 antitrypsin deficiency as predisposing genetic factors [7]. Concerning environmental triggers, most of the CAD are caused by minor neck trauma or manipulation. In literature, previous studies reported an association between CAD and acute and subacute infections [8]. Finally, no conclusive data have been reported for classical vascular risk factors and CAD occurrence. However, hypertension, low level of cholesterol, and low body mass index seem to increase the risk of arterial dissection. Some previous studies showed also the association between migraine and CAD [9]. Figure 1 synthesizes the role and classification of each predisposing and risk factor. Considering isolated intracranial dissections, the aneurysms and the extravascular hemorrhage are specific risk factors, more than in extracranial dissections [10, 11].

The onset of headache or neck pain usually results from the direct tear in the blood vessel wall. The artery has many nerves surrounding them, and for this reason, an irritation due to an injury of their wall provides a cascade of events, including the release of pro-inflammatory neurotransmitters from the nerve terminals. This may cause pain, also far away from the injured arterial site [12].

Headache description and associated symptoms

The 3rd edition of the International Classification of Headache Disorders (ICHD-3) provided specific criteria to identify and diagnose the headache due to CAD [13]. In particular, the association between pain and the diagnosis of arterial dissection is mandatory. Diagnostic criteria are reported in Table 1. Headache could be also associated with neck pain. Reviewing the literature, the headache is the most frequent symptom (up to 100% of cases) and the most frequent inaugural symptom (up to 86% of cases). However, it could be associated with other neurological signs and symptoms, including ipsilateral Horner's syndrome or tinnitus, as usually occur in carotid dissections. Vertigo and nausea are present with the dissections of vertebrobasilar circulation [14]. Another frequent presentation is cerebral ischemia, and the symptoms are consistent with the area of stroke, including vertebral artery dissections that can present with brainstem signs and symptoms [15, 16]. Another less common presentation is the transient monocular visual loss or ischemic optic neuropathy [17].

The systematic review of literature provided 6 papers reporting data considering the headache specific characteristics [18–23]. Literature search methodology is reported in Supplementary Material.

A total of 419 patients were included in the analysis. Headache or neck pain was reported in 295 cases (70.4%) with a prevalence of males (62.3%). Posterior circulation was more frequently described than anterior one (68.2%).

Acute onset of headache was reported in 53% of patients (n. 96/181), and in 87/245 of cases (35.5%), it was the initial symptom of CAD. The intensity of pain was severe in 77/140 patients (55%), while moderate level was registered in 44/140 (31.4% of cases). Overall, the pain was more frequently

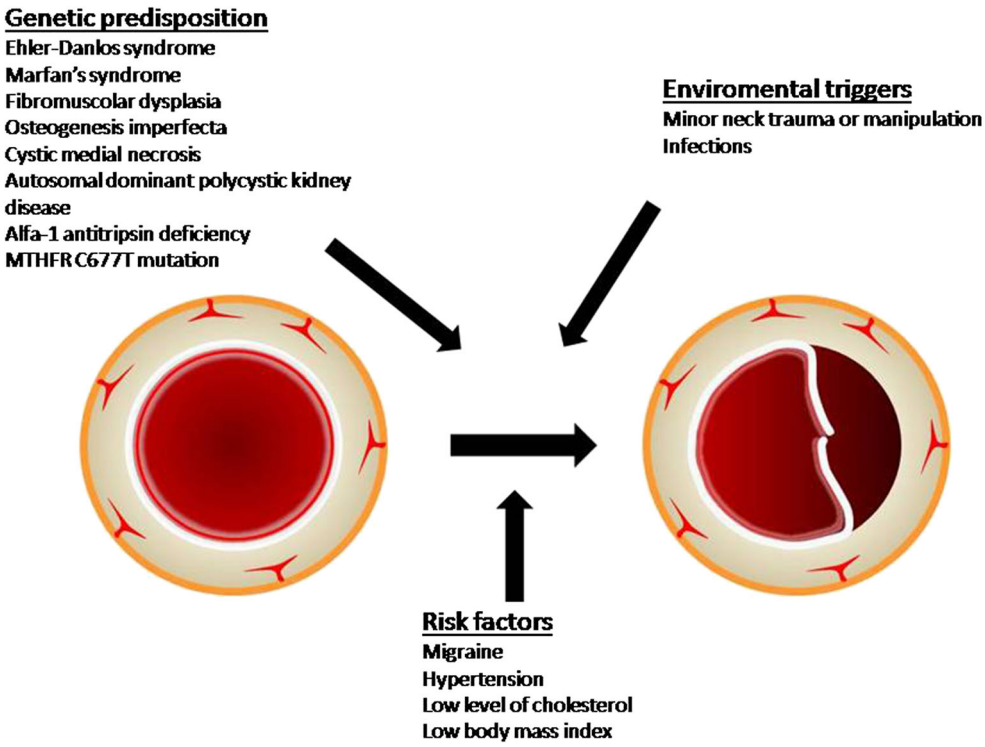

Fig. 1 Predisposing and risk factors for CAD

Table 1 ICHD-3 diagnostic criteria for acute headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection

A. Any new headache and/or facial or neck pain fulfilling criteria C and D
B. Cervical carotid or vertebral dissection has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
  1. Pain has developed in close temporal relation to other local signs of the cervical artery dissection or has led to its diagnosis
  2. Either or both of the following:
    a. Pain has significantly worsened in parallel with other signs of the cervical artery dissection
    b. Pain has significantly improved or resolved within 1 month of its onset
  3. Either or both of the following:
    a. Pain is severe and continuous for days or longer
    b. Pain precedes signs of acute retinal and/or cerebral ischemia
  4. Pain is unilateral and ipsilateral to the affected cervical artery
D. Either of the following:
  1. Headache has resolved within 3 months
  2. Headache has not yet resolved but 3 months have not yet passed
E. Not better accounted for by another ICHD-3 diagnosis

unilateral (n. 99/138, 71.7% of patients). The headache was mainly reported as throbbing (n. 66/188, 35% of cases), followed by pulsating (47/188) and constrictive (n. 31/288). The description of the entire sample from literature is represented in Supplementary Material.

Considering the involvement of anterior circulation, the pain was mainly localized in the temporal region (46% of patients), followed by the frontal area (19.2%). On the contrary, for vertebrobasilar dissections, occipito-nuchal area represented the main interested region by pain (79.7% of cases). Different rates of pain localizations by cranial area and arterial involvement are reported in Fig. 2.

A study reported higher rate of headache in vertebral dissection than in anterior circulation (84.4% vs 74.8%) [24]. Considering the posterior circulation, the proximal involvement was associated to the highest rate of headache with 94.1%. On the contrary, the distal region showed the higher rate of headache in internal carotid artery dissection (80%).

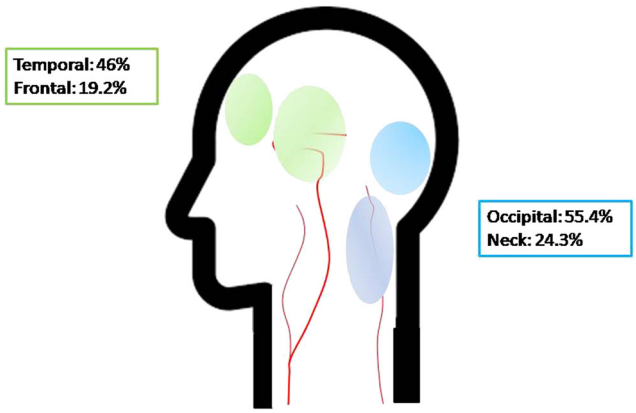

Fig. 2 Localization of headache by arterial involvement. Green, anterior circulation; light blue: vertebrobasilar circulation

One study reported specific differentiation of headache characteristics according to the intracranial and extracranial involvement [18]. In particular, considering intracranial CAD, the intensity of pain is moderate to severe in 36/60 patients with a prevalent localization for temporal and occipital regions for anterior and posterior circulation, respectively. The nature of pain is heterogeneous for carotid involvement, while it is usually throbbing for posterior circulation.

The manifestation of CAD in elderly could be different from the clinical onset in young. A previous study compared some clinical features of patients with CAD by age [25]. Cervical pain and headache rates were significantly different between the two groups of age. The neck pain rates were 45.8% and 27.8% in young and elderly, respectively, while headache was reported in 67.9% and 54.3%.

Diagnosis and treatment

In the case of the suspect for a spontaneous or traumatic arterial dissection, an aggressive diagnostic approach is immediately warranted. The combination of magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are the most direct noninvasive diagnostic modalities to detect an arterial dissection. While it could be difficult to perform these instrumental exams in an emergency setting, the computerized tomography angiography (CTA) is more feasible and may be particularly advantageous for traumatized patients. Digital subtraction angiography remains the gold standard in an accurate definition of this pathological condition, other than it warrants the possibility of an acute stroke treatment, if indicated and necessary. Finally, a first diagnostic bedside approach is represented by the carotid ultrasonography and

Table 2 When should a headache due to CAD be suspected?

- Acute onset, promptly severe, unusual, and unilateral
- Severe intensity for days
- Close temporal relation to other local signs of CAD (i.e., Horner's syndrome)
- Pain worsening in association with other signs of CAD
- Recent trauma or manipulation or prolonged hyperextension of the head
- Presence of genetic predisposing diseases

transcranial Doppler ultrasonography that can provide a direct or indirect evidence of dissection.

Despite the fact that in the case of stroke, an acute treatment using endovenous thrombolysis and/or mechanical thrombectomy is recommended in selected cases, the medical therapy is based both on empiric and clinical observations. Some previous studies and randomized controlled trials (RCT) focused the treatment aim on the secondary prevention, reducing the risk of thrombotic events, particularly artery-to-artery embolism. According to this purpose, the anticoagulation is the most commonly suggested therapy, even if a previous RCT showed no differences between anticoagulants and antithrombotics in reducing stroke recurrences in CAD patients with stroke [26, 27]. The duration and the nature of the treatment are variable. However, in a previous paper, Schievink et al. suggested a complete initial follow-up of 6 months with an intermediate neuroimaging study at 3 months [28]. In the case of a large infarct or an intracranial extension of arterial dissection or an intracranial aneurysm or other contraindications to anticoagulants, an antiplatelet treatment should be introduced and prescribed until the normalization of artery. The same therapeutical approach should be assumed also for anticoagulants.

A previous Italian study showed that headache and migraine associated with CAD improve more than in strokes with other causes [29]. In particular, this symptom disappeared in 14% of patients with the concomitant reduction of frequency, intensity, and the use of anti-migraine medications.

Conclusion

Even if CAD is a relatively rare condition, the dissection represents a high risk for acute cerebrovascular events, especially in young people. The more frequent initial symptom is represented by headache that shows different localizations according to the artery involved (anterior versus posterior circulation). The main characteristics of headache and neck pain are a severe intensity and an acute/subacute onset. In most cases, migraine is associated with other symptoms (i.e., Horner's syndrome or focal signs), increasing the suspect of a CAD and requiring an immediate and accurate diagnostic work-up (Table 2). The headache associated with CAD seems to have a good prognosis with a spontaneous reduction in intensity and frequency, also related to the normalization of arterial patency.

Compliance with ethical standards

Conflict of interest The author declares that he/she has no conflict of interest.

Ethical approval This article does not contain any study with human subjects performed by the author.

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