Medical Hypotheses 80 (2013) 787–790

Contents lists available at SciVerse ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Cervical artery dissection goes frequently undiagnosed

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ARTICLE INFO

Article history:
Received 31 October 2012
Accepted 9 March 2013

ABSTRACT

Cervical artery dissection (CeAD) is a frequent cause of stroke among young patients. It is unclear how many CeADs occur asymptomatically or cause subtle and unspecific clinical symptoms. We hypothesize that CeAD remains often unrecognized. Accordingly, the incidence of CeAD might be higher and the stroke risk lower than generally assumed. Lack of CeAD-indicating clinical symptoms is regarded as the main cause of missed diagnoses. We further hypothesize that underrepresentation of asymptomatic and oligosymptomatic patients in CeAD studies may have biased the association between ischemia and local symptoms in CeAD patients as well as the associations of CeAD with risk factors or co-morbidities. We finally hypothesize that symptomatic CeAD may be preceded by an initial asymptomatic phase. According to this final hypothesis, the time of onset of CeAD should be considered uncertain. The issue of unrecognized CeAD is relevant, as it may affect the associations between CeAD and putative risk factors. Furthermore, the existence of clinically silent CeADs may explain why recurrent and familial CeAD have been rarely observed.

Introduction

CeAD is a common etiology of ischemic stroke in young adults [1]. CeAD does not necessarily cause a stroke, but may present with subtle, transient or unspecific symptoms. It may also occur without symptoms at all. Cervical artery imaging studies occasionally identify unsuspected asymptomatic CeAD [2–5], suggesting that the diagnosis of CeAD with subtle, transient, unspecific or absent symptoms may be missed.

Hypothesis

In the present study we hypothesize that CeAD events occur frequently without being diagnosed. We assume that the likelihood of a CeAD diagnosis depends on the severity and the specificity of the CeAD symptoms. It is furthermore suspected that additional medical conditions and increased health awareness affect the likelihood for the diagnosis, particularly in CeAD patients with subtle symptoms. Our final hypothesis bears on the difficulty to detect the precise time of onset of CeAD: we claim that onset of CeAD symptoms may be preceded by an indefinable initial asymptomatic phase.

Implications

Hypothesis 1. CeAD events remain often unrecognized.

This first hypothesis posits that the incidence of CeAD is higher than assumed and that ischemic symptoms are less common than currently thought. The following data support this hypothesis:

(i) Repetitive MRI investigations of 36 consecutive patients during the first three months after their acute spontaneous CeAD event lead to the identification of 9 patients with a total of 14 recurrent spontaneous CeAD events [6]. Only three patients with recurrent dissections presented with symptoms – which was hemiparesis after stroke in one patient and neck pain in two other patients. The remaining six patients with recurrent CeAD were asymptomatic. In this study, only one out of 14 recurrent CeAD events (i.e., 7%) caused stroke, whereas the majority of CeAD (11 out of 14, 79%) remained without any clinical symptom.

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http://dx.doi.org/10.1016/j.mehy.2013.03.012

(ii) In most patients with multiple dissections, only a single CeAD event causes symptoms. Bilateral vertebral artery dissection (VAD) or bilateral internal carotid artery dissection (ICAD) are typically found in 10–15% of the study samples [7,8]. Interestingly, most patients with two-vessel CeAD present solely symptoms attributable to a single vessel. Ischemic lesions in multiple territories, bilateral Horner syndrome, or bilateral cranial nerve palsy are rare findings [9,10]. In most patients, the additional CeADs were incidental findings during cervical imaging. If we assume that the observed stroke risk for recurrent CeAD (7%) is an unbiased estimate for the overall stroke risk of CeAD, stroke would be rare upon CeAD. However, in CeAD study samples about 60–70% presented with stroke and about 80% with any brain ischemia, including TIA [1,12,14]. We propose that non-ischemic CeAD remained frequently unrecognized.

(iii) In a case study of 12 patients with multiple (triple or quadruple) CeAD events [11], eight patients (67%) had suffered stroke. It may seem disturbing – or at least puzzling – that stroke is equally common among patients with multivessel and single-vessel CeAD. If we assume that each CeAD event is an independent risk for ischemic brain injury, the stroke risk of four-vessel CeAD is expected to be far higher than the stroke risk of single-vessel CeAD (given a stroke risk of 7% upon single-vessel ICAD or VAD, the stroke risk of four-vessel CeAD is estimated to be $1-(1-0.07)^4$ = ca. 25%). Accordingly, multiple CeAD is more likely to cause cerebral ischemia than single vessel CeAD. As a consequence, patients with single-vessel CeAD are more likely to be asymptomatic than patients with multiple CeAD. Unfortunately, CeAD study samples do not permit to detect this clinically important difference between single and multivessel CeAD, since most asymptomatic patients remain unrecognized.

It is interesting to note that most recurrent CeADs are detected within the first month after acute CeAD [6], which is the period of repeated cervical imaging studies. Long term recurrent CeAD, on the contrary, was reported to be very rare [1]. During subsequent years, many asymptomatic events may probably be missed, because cervical imaging studies are less frequently performed.

Hypothesis 2. CeAD diagnosis depends on the severity and specificity of the presenting symptoms.

This assumption implies that asymptomatic patients and patients with very mild symptoms are virtually absent from study samples. Absence of asymptomatic patients may artificially increase the prevalence of presenting symptoms of CeAD patients. More importantly, it may affect the inverse associations that were found among presenting symptoms of CeAD.

In a study of 55 non-ischemic and 145 ischemic ICADs in 181 patients [12], 29 non-ischemic dissections (53%) caused Horner syndrome, compared to 40 ischemic ones (28%, $p < 0.001$). Hence, absence of ischemia was strongly associated with presence of Horner syndrome. We may try to find a biological explanation for these findings and relate them to the pathology of the dissected vessel wall: perhaps an eccentric hematoma is more likely to compress and impair surrounding sympathic nerves whereas subintimal hemorrhage is more likely to cause stenosis and ischemia. On the other hand, the lower likelihood to recruit CeAD patients without stroke compared to those with stroke may also cause an inverse association between Horner syndrome and ischemia. To reach similar frequency of Horner syndrome in non-ischemic as in ischemic ICAD events (28% in the aforementioned study), a simulated addition of 50 hypothetical asymptomatic ICAD events would be needed. (It may be worth noting that patients with minor and unspecific symptoms are also likely to be underrepresented in this study sample – the true number of added asymptomatic patients in this simulation should therefore be even higher.)

Our hypothesis of a spurious inverse association between ischemic CeAD and Horner syndrome has clinical relevance. If we admit that the vessel wall pathology underlying ischemic stroke differs from the vessel pathology causing local symptoms, the presence of local symptoms would indicate a reduced risk for stroke. On the contrary, if the inverse association between ischemia and Horner syndrome is caused by sampling bias – as posited by our hypothesis – there is no association between the presence of local symptoms and the risk for stroke.

Missed diagnosis of patients with absent or mild symptoms may throw light on observed differences between patients with internal carotid artery dissection (ICAD) and vertebral artery dissection (VAD). In the CADISP database, stroke was more common in VAD patients than in ICAD patients [8]. Horner syndrome and cranial nerve palsy may have led to the diagnosis of non-ischemic ICAD patients, whereas non-ischemic VAD patients are mainly identified due to pain. We suspect that non-ischemic VAD patients are more likely to be missed, compared to non-ischemic ICAD patients. As a consequence, in study series stroke is more common upon VAD than upon ICAD.

Hypothesis 3. Patients with additional health problems along with subtle CeAD symptoms are more likely to visit a doctor than patients with subtle CeAD symptoms alone.

On top of the strong inverse associations between stroke and local signs, or pain in patients from the CADISP database (low Odd Ratios in Table 1), the observed Odd Ratios for the associations with hypertension, hypercholesterolemia, migraine, preceding trauma and preceding infection were also slightly below 1. Apparently, hypertension, hypercholesterolemia, migraine, and a history of mild trauma or infections were more prevalent among non-ischemic CeAD patients. We consider the slightly increased prevalence of risk factors among non-ischemic patients as potentially artificial for several reasons:

(i) Patients with severe stroke may incompletely report risk factors, due to aphasia or disturbances of memory [14]. As a consequence, the reported prevalence of risk factors in the CeAD patients with stroke might be underestimated.

(ii) The diagnosis of CeAD in non-ischemic patients may be more likely, if the patients have additional complaints. Minor trauma or a respiratory tract infection may lower the threshold of a visit to the doctor. The well-recognized association of CeAD with trauma or infections may therefore be inflated by the fact that non-ischemic CeAD patients are more likely to be diagnosed when they have a history of minor trauma or infections.

(iii) In case-control studies, part of the invited control subjects usually declines participation (non-responders). We hypothesize that subjects with recent trauma or infections or with co-morbidities like migraine or obesity are less likely to be included as control subjects, compared to healthy subjects without trauma, infections, migraine or obesity. As a consequence, the associations with trauma, infections, migraine or hypertension may in reality be weaker than suggested by the observations from clinical study samples.

Hypothesis 4. The time of onset of CeAD is frequently uncertain, since a hypothetical initial asymptomatic course may have occurred.