Cervical artery dissection in patients ≥60 years

Often painless, few mechanical triggers

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Supplemental data at Neurology.org

ABSTRACT

Objective: In a cohort of patients diagnosed with cervical artery dissection (CeAD), to determine the proportion of patients aged ≥60 years and compare the frequency of characteristics (presenting symptoms, risk factors, and outcome) in patients aged <60 vs ≥60 years.

Methods: We combined data from 3 large cohorts of consecutive patients diagnosed with CeAD (i.e., Cervical Artery Dissection and Ischemic Stroke Patients–Plus consortium). We dichotomized cases into 2 groups, age ≥60 and <60 years, and compared clinical characteristics, risk factors, vascular features, and 3-month outcome between the groups. First, we performed a combined analysis of pooled individual patient data. Secondary analyses were done within each cohort and across cohorts. Crude and adjusted odds ratios (OR [95% confidence interval]) were calculated.

Results: Among 2,391 patients diagnosed with CeAD, we identified 177 patients (7.4%) aged ≥60 years. In this age group, cervical pain ($OR_{adjusted}$ 0.47 [0.33–0.66]), headache ($OR_{adjusted}$ 0.58 [0.42–0.79]), mechanical trigger events ($OR_{adjusted}$ 0.53 [0.36–0.77]), and migraine ($OR_{adjusted}$ 0.58 [0.39–0.85]) were less frequent than in younger patients. In turn, hypercholesterolemia ($OR_{adjusted}$ 1.52 [1.1–2.10]) and hypertension ($OR_{adjusted}$ 3.08 [2.25–4.22]) were more frequent in older patients. Key differences between age groups were confirmed in secondary analyses. In multivariable, adjusted analyses, favorable outcome (i.e., modified Rankin Scale score 0–2) was less frequent in the older age group ($OR_{adjusted}$ 0.45 [0.25, 0.83]).

Conclusion: In our study population of patients diagnosed with CeAD, 1 in 14 was aged ≥60 years. In these patients, pain and mechanical triggers might be missing, rendering the diagnosis more challenging and increasing the risk of missed CeAD diagnosis in older patients. *Neurology*® 2017;88:1313–1320

GLOSSARY

CADISP-Plus = Cervical Artery Dissection and Ischemic Stroke Patients–Plus; **CeAD** = cervical artery dissection; **CI** = confidence interval; **IPD** = individual patient data; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio.

Cervical artery dissection (CeAD) is uncommon in the general population, but it is a major cause of stroke in the young.[1,2] The majority of patients with CeAD are aged 40–50 years at CeAD occurrence.[1,3] In patients aged 60 years and above, atherosclerosis, small vessel disease, or cardioembolism dominate as mechanisms of ischemic stroke.[4] Although there are few reports

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about CeAD in patients in their 60s and 70s,[5,6] the frequency of characteristics (presenting symptoms, risk factors, and outcome) in this age group of patients with CeAD remains unknown.

The profile of patients with CeAD seems to be different in younger and older age groups.[7] For CeAD patients ≥60 years, an age group where CeAD is considered less frequent, it remains unknown if clinical characteristics, vascular findings, and 3-month outcome differ compared to younger patients. Such data are clinically important: first, CeAD is commonly thought of as a disease in the young[1] and therefore clinicians might not consider CeAD in older patients. Second, knowledge of the characteristics of CeAD for patients ≥60 years is important to inform appropriate diagnostic and treatment decisions in the older age group.

With these considerations in mind, we aimed to (1) determine the proportion of patients with CeAD aged ≥60 years and (2) identify the characteristics of patients with CeAD aged ≥60 years compared to those aged <60 years. We analyzed the extended dataset of the multicenter Cervical Artery Dissection and Ischemic Stroke Patients–Plus (CADISP-Plus) consortium.[8,9]

METHODS

Study population and data collection. The updated dataset of the multicenter CADISP-Plus consortium comprises 2,426 patients with CeAD including patients from the CADISP clinical study (CADISP-1 cohort: n = 983 patients and CADISP-2 cohort [US centers]: n = 312 patients) and the Paris-Lariboisière/Zurich/Bern CeAD registry (n = 1,131 patients). The detailed structure and methods of each of these clinical cohorts have been described in detail.[9–11] All sites from these cohorts applied the same widely accepted diagnostic CeAD criteria and definitions of key variables allowing pooled analyses.[8] There was, however, no standardized surveillance across cohorts and age groups (i.e., standardized assessments were not uniformly performed on all stroke patients to assess for CeAD). In brief, diagnostic criteria of CeAD (for internal carotid or vertebral artery) were defined as follows: presence of a mural hematoma, aneurysmal dilation, long tapering stenosis, intimal flap, double lumen, or occlusion situated >2 cm above the carotid bifurcation revealing an aneurysmal dilation or a long tapering stenosis after recanalization.[8] An overview of the cohorts is given in the e-Methods at Neurology.org.

Patient characteristics and variable definitions. The following demographic, clinical, and imaging data were obtained for individual patients from each cohort as done in previous research[8,12,13]: age, sex, vascular risk factors according to predefined criteria (i.e., presence or absence of hypertension, hypercholesterolemia, and diabetes),[14] site of dissection (i.e., internal carotid artery, vertebral artery, both internal carotid and vertebral artery),[15] pathologic features of the dissected artery (i.e., presence or absence of a vessel occlusion),[15] presenting symptoms including ischemic stroke, TIA, and local signs and symptoms (i.e., Horner syndrome, headache, and cervical pain),[13] presence or absence of putative CeAD risk factors (i.e., migraine[16] and prior mechanical trigger events[12]), and stroke severity as assessed by the NIH Stroke Scale score (NIHSS). Functional outcome was assessed during outpatient visits or telephone calls using the modified Rankin Scale (mRS) at 3 months. Excellent functional outcome was defined as an mRS score of 0–1, favorable outcome as an mRS score of 0–2. Patients with a history of polytrauma within the prior 4 weeks were excluded from the current analysis. Detailed definitions of each of these variables were published previously.[8,9,11]

Statistical analyses. Patient baseline demographic and clinical data were compared between patients with CeAD aged ≥60 years and those <60 years. First, we compared variables between groups (i.e., ≥60 vs <60) across all patients from every cohort in the form of a combined analysis based on pooled individual patient data (IPD). For categorical variables, differences between groups were assessed using the χ^2 test, or the Fisher exact test if suitable. Differences in continuous variables were calculated using the Mann-Whitney test. Multivariable logistic regression analysis was performed with adjustment for sex and site of dissection (i.e., internal carotid vs vertebral artery dissection).[7] For analysis of 3-month outcome, we adjusted for stroke severity (NIHSS) and occlusion of the dissected artery as the most important outcome predictors in CeAD.[17] Based on the results of the univariate analyses, we also adjusted for diagnoses of hypertension and hypercholesterolemia. A p value <0.05 was considered statistically significant.

For the secondary analyses, we performed (1) univariate and adjusted multivariable comparisons between age groups within each separate cohort and (2) meta-analyses across all 3 clinical cohorts by using a fixed-effects Mantel-Haenszel model with calculation of odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Heterogeneity across study cohorts was assessed using the I^2 index. As post hoc analyses we compared patients aged ≤45 years to those aged ≥65 years in unadjusted, univariate comparisons on the IPD dataset.

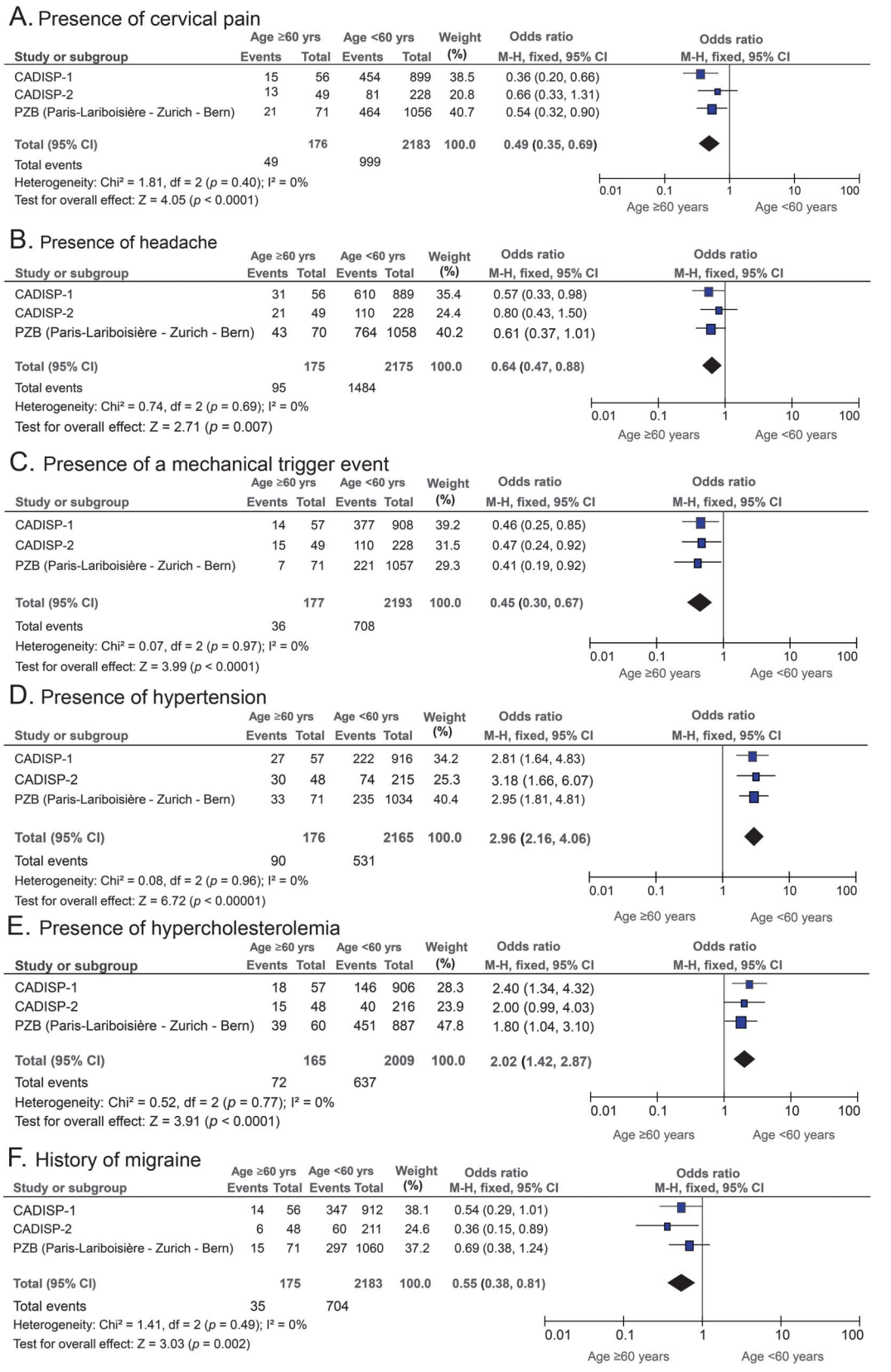
Standard protocol approvals, registrations, and patient consents. Local authorities and ethics committees approved protocols for the included cohorts from all participating centers. Data collection and analyses were conducted according to national rules of approval and informed consent of the included patients.

RESULTS

Patient demographics. A total of 2,391 patients with CeAD out of 2,426 patients were eligible for analysis. Among these, we identified 177 (7.4%) patients aged ≥60 years. The overall median age of all consecutive patients with CeAD included in this study was 45 years (interquartile range 38–52). Patient demographics and clinical characteristics are presented in table 1 (across all patients) and tables e-1 through e-3 (separately for each study cohort). In patients aged ≥60 years, male patients were predominant (67.8% of those ≥60 years old vs 55.8% <60 years old; $p_{\text{unadjusted}} = 0.002$; table 1).

Patient clinical characteristics and putative risk factors. ***Combined analysis of pooled IPD and meta-analysis across study cohorts.*** Patients aged ≥60 years presented less

Figure 1 Forest plots of the meta-analyses across all 3 clinical cohorts (Cervical Artery Dissection and Ischemic Stroke Patients [CADISP]-1, CADISP-2, and Paris-Lariboisière/Zurich/Bern CeAD registry [PZB])



(A–F) Frequency of patient characteristics were compared between patients aged ≥60 years and <60 years. A fixed-effects Mantel-Haenszel (M-H) model was used, with calculation of unadjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Heterogeneity across study cohorts was assessed using the I^2 index. Results of those analyses showing significant differences between the age groups are presented.

frequently with cervical pain or headache (cervical pain, IPD: $OR_{adjusted}$ 0.47 [0.33–0.66]; headache, IPD: $OR_{adjusted}$ 0.58 [0.42–0.79]) (table 1 and figure 1). In contrast, an equal proportion of patients in each age group presented with Horner syndrome (31.3% [≥60 years] vs 30.2% [<60 years]). This held true for Horner syndrome in the absence of pain, other local signs of CeAD (i.e., tinnitus, cranial nerve palsy), or mechanical trigger events (n = 8 [20%, age ≥60 years] vs n = 54 [26.7%, age <60 years], $p_{unadjusted}$ = 0.884). Likewise, cerebral ischemic events (i.e., ischemic stroke or TIA) at CeAD onset occurred at similar rates in both young and older patients with CeAD (table 1 and figure e-1).

Mechanical trigger events prior to CeAD onset were significantly less common in patients aged ≥60 years (IPD: $OR_{adjusted}$ 0.53 [0.36–0.77]; table 1). Migraine was also less frequent in older patients with CeAD (IPD: $OR_{adjusted}$ 0.58 [0.39–0.85]; table 1). In contrast, hypercholesterolemia (IPD: $OR_{adjusted}$ 1.52 [1.1–2.10]), hypertension (IPD: $OR_{adjusted}$ 3.08 [2.25–4.22]), and diabetes (IPD: $OR_{adjusted}$ 3.8 [2.09–6.93]) were more common in patients with CeAD aged ≥60 years.

For the distribution of the site of dissection (internal carotid or vertebral artery), as well as the occlusion of the dissected artery, there was no significant difference between the 2 age groups in primary (IPD) or secondary analyses (table 1, tables e-1 through e-3, and figure e-1). Post hoc analyses of the first antithrombotic treatment after CeAD diagnosis revealed the following results: overall, 2,191 patients (91.6%) received any antithrombotic therapy after diagnosis of CeAD (n = 164 [92.7% of patients aged ≥60] and n = 2,027 [91.6% of patients aged <60]). Anticoagulants were used significantly less often in patients aged ≥60 years (patients receiving anticoagulants: n = 82 [50%, age ≥60] vs n = 1,295 [63.9%, age <60], $p_{unadjusted}$ <0.001).

Unadjusted analysis of favorable functional outcome (i.e., mRS 0–2) at 3 months did not show a difference between the age groups (IPD: $OR_{unadjusted}$ 0.71 [0.45–1.10]). However, after adjustment (for sex, site of dissection, occlusion of the dissected artery, NIHSS, hypertension, and hypercholesterolemia), the analysis revealed a lower likelihood of a favorable outcome in patients with CeAD aged ≥60 years (IPD: $OR_{adjusted}$ 0.45 [0.25, 0.83]) (table 1).

Key findings on differences between age groups showed similar results in primary analyses (of combined data and within each cohort) as well as the secondary analyses (in meta-analyses across cohorts). To look for extremes of effect, we further performed unadjusted post hoc analyses comparing characteristics of patients aged ≤45 years to those aged ≥65 years (i.e., removing those aged 46–64 years old). We focused on variables that showed statistically significant differences between age groups in our primary analyses. This post hoc analyses mainly confirmed our primary results, with all associations being in the same direction of effect, and only the frequency of mechanical trigger events losing significance ($p_{unadjusted}$ = 0.073; table e-4).

Detailed information on the distribution of characteristics and risk factors are given in table 1 and tables e-1 through e-4, as well as figure 1 and figure e-1.

DISCUSSION In this large compilation of individual data of patients diagnosed with CeAD, our analyses on proportion and characteristics of patients with CeAD aged ≥60 years revealed the following key findings. First, 7% of the patients with CeAD in our study population were aged ≥60 years. Second, in the studied population, compared to those aged <60 years, patients with CeAD aged ≥60 years were more often male, but were less likely to have painful CeAD, a preceding mechanical trigger event, or a history of migraine. Third, in this population, age ≥60 years was independently associated with less favorable outcome after CeAD.

Until now, the frequency of patients aged ≥60 years among patients with CeAD has not been systematically studied. In a small CeAD cohort, over 30% (11 of 34) of patients with CeAD were reported to be aged >60 years.[6] Although limited by a small sample size, this number indicated that CeAD in elderly patients might occur more frequently than suspected in a disease characterized as primarily affecting younger age groups.[1–3] Our analysis of a large, multicenter dataset found that 1 out of 14 patients with CeAD was 60 years or older. The 95% CI (6.4–8.5) in our analysis indicated that this rate could even be as high as every 11th CeAD patient. In addition, there was a clear male preponderance in this age group, in line with previous findings.[7]

Cervical pain and headache are common local symptoms in patients with CeAD.[11,15] However, our analysis revealed that cervical pain is not a hallmark of CeAD in patients ≥60 years. We can only speculate on the reasons for this observation. Pain in CeAD most likely arises directly from the irritation of nerves surrounding the dissected vessel.[18,19] An age-related decrease in nociceptors might be a hypothetical explanation for this observation. In addition, there is evidence of the association of increasing age with increasing arterial (carotid) stiffness.[20] Increasing arterial stiffness in older patients leading to a decreased distensibility of the cervical arteries may play a role in a reduction of periarterial nerve irritation in CeAD and thereby a reduction of painful local symptoms.

Older patients with CeAD less frequently report a history of migraine. Migraine—in particular without aura—has been associated with CeAD in prior studies. Compared to age- and sex-matched ischemic stroke patients without CeAD, a history of migraine was significantly more common among patients with CeAD.[16,21] In the general population, migraine is most common among middle-aged adults,[22] and it is more common among female patients.[22,23] Thus, the effect seen in our analysis may reflect the age and sex distribution of migraine in the general population. In turn, hypertension and hypercholesterolemia were significantly more common among older patients with CeAD compared to younger ones. In general, compared to age- and sex-matched healthy referents, patients with CeAD are more frequently hypertensive but show a lower prevalence of hypercholesterolemia.[14]

In patients with CeAD aged ≥60 years, mechanical trigger events were reported only in one fifth of patients, which is significantly less frequent than in younger patients (one third). Mechanical trigger events seem to play an important role in CeAD pathophysiology, as they are significantly more prevalent in CeAD as compared to ischemic stroke patients without CeAD and healthy subjects.[12] The underlying reason for a lower frequency of such trigger events in older patients remains elusive. It might point at a less physically active lifestyle of older patients, thereby reducing the risk of CeAD in older individuals. However, age-dependent differences in pathophysiology of CeAD cannot be ruled out. For instance, the dissecting mechanism of CeAD in older patients may arise intrinsically in the artery rather than from external forces.[24] Further, mechanical trigger events, in particular minor traumas, may play a subordinate role in older patients with CeAD as the arteries may be less susceptible to mechanical stress given the increased arterial stiffness in older patients.

Our observation that patients with CeAD aged ≥60 often lack pain and mechanical trigger events —characteristics considered suggestive for CeAD— indicates the possibility that CeAD might be underdiagnosed in this age group. Compared to younger patients, investigations to diagnose CeAD might be ordered less often in this age group, as CeAD is considered a disease of young to middle-aged adults and typical clinical CeAD signs and symptoms seem infrequent in those aged ≥60 years. Signs of CeAD in routine neurovascular imaging might be subtle. The likelihood of clinicians missing or overlooking such subtle signs, or of performing incomplete vascular imaging, might be increased if clinicians do not consider CeAD as potential cause of symptoms.

In our cohort, patients with CeAD aged ≥60 had less favorable outcome than younger patients, which is in line with findings in ischemic stroke patients without CeAD.[7]

A major strength of our study is the large sample size, which reduces the risks of chance findings and allows adjustment for potential confounders. Further, the design of our analyses proves that our findings are solid: the major results of the IPD were confirmed by analyses within each separate cohort as well as by meta-analyses across all 3 cohorts. Moreover, baseline characteristics and outcomes have been collected according to standardized criteria irrespective of and therefore unbiased by the present research question.

Still, we are aware of the following limitations: (1) the data used in this analysis are based on large hospital-based cohorts of CeAD patients, which are non-randomized and were not monitored; (2) the size of the age groups differs considerably; (3) our dataset did not comprise information on the presence of genetic factors, precluding analyses on the role of such factors in age subgroups or the interaction with acquired risk factors; and (4) there were no predefined surveillance procedures in the study cohorts, which may lead to an ascertainment bias. As a consequence, the age distribution found in our cohorts may not represent the true distribution in CeAD. In addition, differential ascertainment based on different exposures and risk factors in the different age groups might impair the reliability of our findings on the frequency of risk factors and clinical characteristics within each age group. We acknowledge that our data do not allow us to define strict criteria on which patients should undergo a specific evaluation for CeAD, in particular since we did not include a comparison group of patients without CeAD. For the latter reasons, we were unable to provide data on the frequency of CeAD in all stroke patients aged ≥60.

Our analyses of large hospital-based cohorts of patients diagnosed with CeAD in departments of neurology in tertiary hospitals suggest that in this setting 1 in 14 patients with CeAD is aged ≥60 years. Compared to younger age groups, CeAD in persons aged ≥60 years is more often painless and lacking identifiable mechanical trigger events, which renders the diagnosis more challenging. As older patients with CeAD may have less favorable outcomes, it is important to be aware of the risk and consider CeAD among other more frequent stroke subtypes in these age groups.

AUTHOR CONTRIBUTIONS

C.T. designed/conceptualized the study, analyzed/interpreted the data, drafted the manuscript, and collected data. M.A. supervised the study, analyzed/interpreted the data, revised the manuscript, and collected data. S.T.E. initiated, designed, conceptualized, and supervised the study, analyzed/interpreted the data, revised the manuscript, and collected data. All authors collected data, performed critical review of the manuscript, and edited the manuscript for content.

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