Cerebrovascular Diseases

Original Paper

Familial Occurrence of Cervical Artery Dissection – Coincidence or Sign of Familial Predisposition?

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Abstract

Background and Purpose: The etiology of spontaneous cervical artery dissection (CeAD) is poorly understood in most patients. Mild cervical trauma preceding the dissection event is a common finding, but many CeAD occur spontaneously. It is likely that genetic factors may increase the risk for CeAD. However, familial cases are excedingly rare. Familial clustering of CeAD may be accidental or associated with genetic or environmental risk factors shared between affected relatives. In this explorative study, we aim to show that specific risk factors for familial CeAD exist. **Methods:** Age of onset, sex, affected artery and number of recurrent CeAD were documented for familial patients and compared with published findings from patients with sporadic CeAD. Concordance of age, sex and dissected artery within the families was analyzed by correlation analysis and by analysis of variance or Kruskal-Wallis testing. **Results:** The study sample consisted of 9 new patients with a family history of CeAD enrolled in the Neurology Department of the University of Heidelberg or referred to Heidelberg from other centers. The study sample also included published findings from another 23 patients, in total 32 patients. The mean age of the patients with familial CeAD at their first dissections was 38.4 ± 13.3 years. Twenty (62.5%) patients were female and 12 patients (37.5%) suffered multiple dissections. Four patients (12.5%) presented with recurrent dissections after >1 year. Patients with a familial history of CeAD were younger (p = 0.023) and presented more often with multiple dissections (p = 0.024) and recurrent dissections (p = 0.018). Age at the first event (correlation analysis p = 0.026; analysis of variance p = 0.029) and site of the dissection (correlation analysis p = 0.032; Kruskal-Wallis test p = 0.018) differed between the families, and there was no concordance of gender of affected family members (correlation analysis p = 0.500; Kruskal-Wallis test p = 0.211). **Conclusions:** The high prevalence of multiple dissection events and of long-term (>1 year) recurrent dissections in patients with a familial history of CeAD indicates that a specific predisposition for familial CeAD exists. Since age of onset and affected vessel differ between families, the risk profile for familial CeAD is heterogeneous. A large-scale (whole exome) sequencing analysis of 14 patients from 7 of the analyzed families is currently being performed in order to identify causative genetic variants.

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Introduction

Dissection of cervical arteries (CeAD) is a leading cause of stroke in patients below 50 years of age. The etiology of CeAD is poorly understood in the majority of the patients. Mild cervical trauma preceding the dissection event is a common finding, but many CeAD occur spontaneously [1, 2]. Hypertension, migraine, low body mass index, hypocholesterolemia and mild hyperhomocysteinemia are associated conditions [3–6]. Some authors assume that genetic factors may increase the risk for CeAD, although familial cases are very rare and genetic risk variants have not yet been identified [7]. Most patients showed alterations of the dermal connective tissue in mild to moderate form [8, 9]. This connective tissue phenotype followed an autosomal dominant pattern of inheritance in some analyzed families [9, 10]. In the current study of patients with a familial history of CeAD, we searched for characteristic findings of familial CeAD and tested for concordance of age and of affected vessel within the families.

Patients and Methods

CeAD patients with a family history of CeAD were identified and treated in neurology departments of different centers between 2004 and 2011. All affected patients were examined by a stroke neurologist. Only families for which we had clinical data from all affected family members were included. Patients were carefully screened for signs of known hereditary connective tissue disorders (Marfan-like appearance, joint hypermobility, skin hyperextensibility, poor wound healing, thin translucent skin, blue sclerae and varices). Only patients with familial CeAD were considered, whereas patients or relatives with dissections or aneurysms in other parts of the arterial tree were not included. Published findings from patients with a familial history of CeAD [11, 12] were included in the analysis and compared with published findings from sporadic CeAD patients [13–16]. Mean age of CeAD patients was ≥44 years (estimated at 44.1 [16], 45.4 [13], 44.0 [14], or 44.9 years [12]), with at least 50% men (56.7% [16], 57.3% [13], 52.9% [14], or 48% [12]), with a frequency of less than 20% of multiple dissections (estimated at 11.9% [15], 12.1% [13], 15.7% [14], or 25% [17]) and with a frequency of long-term recurrent dissections below 3% (estimated at 0.9% [14]). A recurrent dissection was defined as any new dissection in a cervical artery.

By one-dimensional ANOVA or its nonparametric equivalence, the Kruskal-Wallis test, we tested for heterogeneity between affected families concerning age at the first event, sex and localization of the dissection (carotid artery vs. vertebral artery). Significant test results indicate that at least one of the families is different from the other families, regarding age of onset (ANOVA), or localization of the dissection (Kruskal-Wallis). As an alternative approach to calculate the concordance between the

family members we used bivariate correlation analysis of the families with 2 affected persons and of the sister and cousin of family 5 and the 2 daughters of family 6. The SPSS (version 19) software package was used for statistical analysis. Occurrence of multiple events and recurrent events in familial and sporadic patients was compared with the χ^2 test of goodness of fit. p values were calculated for upper estimates of 20% multiple events and 3% long-term recurrent events in the population of sporadic CeAD patients.

The study was approved by the ethics committees and by other authorities in each participating center according to local rules. All participants gave informed consent.

Results

Nine patients with a familial history of CeAD were included. Eight patients belonging to 4 families were diagnosed between 2004 and 2011. An affected member of a fifth family who was described before was also analyzed as well as published findings from 23 patients with a history of CeAD (table 1). None of the patients showed signs of a known connective tissue disorder. Magnetic resonance angiography revealed a clinically asymptomatic carotid pseudoaneurysm in the father of the affected sisters from family 2.

Patients with a family history of CeAD had a mean age of 38.4 ± 13.3 years at onset of the first event. Twenty patients (62.5%) were women, 12 (37.5%) suffered from multiple CeAD events, and 4 (12.5%) patients had recurrent dissections after a delay of more than 1 year (table 2). Compared to published findings from (foremost) sporadic CeAD, patients with a family history of CeAD were younger and suffered more multiple dissections, particularly more long-term recurrencies. By variance analysis and Kruskal-Wallis analysis we tested the null hypothesis of no difference concerning age of onset, arterial localization (vertebral vs. internal carotid artery) or sex between the families. The age of the patients varied less within families, compared to the variance of age between the families (one-dimensional ANOVA p = 0.029; correlation = 0.591, p = 0.026), indicating intrafamilial concordance of age. Hence, the age of onset of CeAD in one family member predicts the age of onset in the related family members. The risk to develop a dissection in a particular artery was not independent of the localization of dissection in the affected relatives (Kruskal-Wallis test p = 0.018; Spearman rho = 0.555, p = 0.032). There was no concordance of gender of affected relatives within a family (Kruskal-Wallis test p = 0.211; Spearman rho = 0.189, p = 0.500).

Table 1. Patients with a familial CeAD

Family		Gender	Relationship	Age	Location	Recurrent CeAD (delay after first event in years)
1	(Germany)	f	mother	49	ICA-le	
		f	daughter	31	ICA-ri	
2	(Brazil)	f	sister	36	ICA-ri	ICA-le (1.5)
		f	sister	37	ICA-le	
3	(Germany)	f	sister	39	ICA-ri, ICA-le	
		m	brother	45	ICA-le	
4	(Germany)	m	brother	43	ICA-le	
		f	sister	41	ICA-le	
5	[11]	f	sister	19	ICA-ri	
		f	cousin	18	ICA-ri	
		f*	sister/cousin	32	ICA-ri, ICA-le, VA-ri	
6	[11]	m	father	55	ICA-ri	
		f	daughter	38	ICA-ri, ICA-le	
		f	daughter	32	ICA-le	
7	[11]	m	brother	29	VA-le	
		f	sister	27	VA-le, VA-ri	
8	[11]	m	father	31	ICA-le	
		m	son	31	VA-le	VA-ri (2), VA-ri (3) ICA-ri (5), ICA-le (7)
9	[11]	f	sister	59	ICA-le	
		m	brother	49	CCA+ICA-le	
10	[11]	f	sister	36	VA-ri	
		f	sister	38	VA-ri	
11	[11]	f	mother	53	ICA-le	
		f	daughter	28	ICA-ri, ICA-le	
12	[12]	f	mother	35	ICA-le, ICA-ri	
		f	daughter	18	ICA-ri	ICA-le (5.3)
13	[12]	m	father	76	ICA-ri	
		m	son	47	ICA-ri, ICA-le	
14	[12]	m	cousin	63	ICA-le	
		m	cousin	43	VA (affected side not reported)	
15	[12]	f	sister	25	VA-le	VA-ri (6.6)
		m	brother	25	ICA (affected side not reported)	

CCA = Common carotid artery; ICA = internal carotid artery; VA = vertebral artery; le = left; ri = right. Asterisk = patient recruited during the current study. [11], [12] = families described in references 11 and 12 of this study.

Table 2. Age, sex and the occurrence of multiple dissection events in sporadic and familial cases

	Study sample of familial CeAD	Sporadic CeAD	p
Age, years	38.4 ± 13.3	≥44	0.023*
Female sex	20 (62.5%)	≤50%	0.16**
Multiple CeAD	12 (37.5%)	≤20%	0.024**
Late recurrence	4 (12.5%)	≤3%	0.018**

Characteristics of sporadic CeAD according to the literature [13–15]. * p value calculated with t test for a single sample and a test value of 44 years; ** p values calculated with χ^2 test of goodness of fit with 50% expected male patients, 20% expected multiple events and 3% expected recurrent events.

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Discussion

Familial clustering of CeAD is probably not purely accidental. Two of the 15 families had 3 affected relatives, and an asymptomatic father from a third family had a pseudoaneurysm that might have been developed from possible CeAD [1]. In this study, patients with a family history of CeAD were younger, most were women and multiple dissections were frequent. Patients with sporadic CeAD may suffer multiple dissections within a short vulnerable episode of 1–3 months [17], but recurrent events after a longer delay are rare [14]. The statistical comparison of familial and sporadic patients is of limited value. The study sample of patients with familial dissections was small and selected. More importantly, sporadic and familial patients were not sampled from the same population. Moreover, the study populations of sporadic patients used for comparison (the Swiss-Paris study sample [13], the French multicenter study sample [14] and the CADISP study sample [15, 16]) contain very few patients with familial CeAD, and may have possible overlap. Hence, the lower age of onset, the significant enrichment of multiple dissections and recurrent dissections among familial patients deserve validation. It seems likely that the diagnosis of CeAD may be easily missed in patients with minor or transient clinical symptoms. A second affected case within a family will be more likely to be identified since the disease and its symptoms are known and affected family members will be more prone to visit a doctor even with mild clinical symptoms. It cannot be excluded that some rare cases of familial CeAD were missed in earlier publications [18], as mentioned in Martin et al. [11].

It might be speculated that the risk for CeAD is dependent on a particular combination of different risk alleles. As it is unlikely that particular combinations of alleles segregate within a family, the disease is in most cases sporadic, although genetic factors do play a role. The finding of an inherited connective tissue phenotype in families, derived from skin biopsies from sporadic CeAD patients, revealed that healthy relatives of sporadic patients may show a subclinical phenotype [9, 10]. However, clinically overt connective tissue aberrations were not detectable in most patients with a family history of CeAD [11]. The nature of the familial predisposition for CeAD remains currently unknown.

Whereas the differences between sporadic and familial patients pointed to specific risks for familial CeAD, the analysis of age, sex and affected site revealed significant differences between the affected families. We speculate that the predisposition for familial CeAD is heterogeneous. Families may carry causative Mendelian mutations in different candidate genes like COL3A1 (encoding type III collagen), TGFBR2 (encoding the transforming growth factor beta receptor 2) or COL1A1 [19, 20], possibly interacting with specific environmental or lifestyle factors.

Disclosure Statement

None.

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