Risk of ischemic stroke and total cerebrovascular disease in familial hypercholesterolemia; a register study from Norway

Cover title: Stroke in familial hypercholesterolemia

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Abstract

Background and purpose

Familial hypercholesterolemia (FH) is a common autosomal dominant disease leading to increased level of serum low-density lipoprotein cholesterol and risk of coronary heart disease (CHD). Whether FH increases the risk of cerebrovascular disease including ischemic stroke is debated. Accordingly we studied the incidence of cerebrovascular disease in a cohort of persons with genetically verified FH compared to the entire Norwegian population, and examined whether persons in this cohort with previous cohort had increased risk of cerebrovascular disease.

Methods

Incidence rates of hospitalization for cerebrovascular disease (among 3144 persons with FH) and ischemic stroke (among 3166 persons with FH) were estimated by linkage of FH persons to CVDNOR; a nationwide database of cardiovascular disease hospitalizations (2001-2009). We calculated standardized incidence ratios (SIRs), and used Cox regression to estimate hazard ratios (HRs).

Results

A total of 46 cases (19 women and 27 men) of cerebrovascular disease were observed in the cohort of persons with FH, with no increased risk of cerebrovascular disease compared to the general population (SIR=1.0, 95% confidence interval (CI) (0.8-1.4)). Total number of ischemic strokes in the cohort of persons with FH was 26 (9 women and 17 men), with no increased risk compared to the general population (SIR=1.0, 95%CI (0.7-1.5)). Prior CHD significantly increased cerebrovascular disease risk in women (HR=3.29, 95%CI 1.20-9.00)) but not in men (HR=1.03, 95%CI (0.45-2.37); $p_{interaction}$=0.04).

Conclusions

In a large cohort of genetically verified FH, risks of cerebrovascular disease and ischemic stroke were not increased compared to the total Norwegian population.

Introduction

Stroke is an important cause of disability and death worldwide,[1] and there are several risk factors for stroke such as hypertension, carotid artery atherosclerosis and smoking.[2] Atherosclerosis is an underlying factor for stroke, and accordingly, low-density lipoprotein (LDL)-cholesterol lowering therapy is important in both primary and secondary prevention of cerebrovascular diseases including stroke.[3]

Persons with heterozygous familial hypercholesterolemia (FH) have increased levels of LDL-cholesterol from birth,[4] and increased risk of premature coronary heart disease (CHD) and heart failure due to the increased LDL-cholesterol load.[5–7] With the increased risk of atherosclerosis, the risk of stroke in FH patients is expected to be high. However, whether the risk of stroke in FH patients is increased has been debated and previous studies have yielded inconsistent results.[8, 9]

Our aim was to investigate risk of cerebrovascular disease including ischemic stroke in a genetically verified cohort of persons with FH in comparison with the risk in the entire Norwegian population. In addition, we aimed to examine whether previous hospitalization for CHD was associated with the risk of cerebrovascular disease, including ischemic strokes.

Material and methods

The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway, and is a cohort study of persons with FH identified from the Unit for Cardiac and Cardiovascular Genetics (UCCG) Registry linked to the Norwegian Cause of Death Registry and the Cardiovascular Disease in Norway (CVDNOR) project database. Data used in this project cannot be made available for researchers without new approvals because of data protection legislation in Norway. All patients with genetically diagnosed FH in Norway are included in the National UCCG Registry after written informed consent. Prior to the registry linkage all patients received a letter and were offered to be removed from the list and not participate in the registry linkage.

An incident event of cerebrovascular disease was defined as a hospitalization with cerebrovascular disease as main or secondary diagnosis or death with cerebrovascular disease as the underlying cause, without any prior hospitalizations with cerebrovascular disease during the past seven years. Patients were followed from inclusion in the FH registry until the first occurrence of cerebrovascular disease, death or 31st December 2009, whichever came first. Incident events of ischemic stroke were defined in the same manner.

We calculated incidence rates and standardized incidence ratios (SIRs with 95% confidence intervals (CIs)) for cerebrovascular disease and ischemic stroke using incidence rates for the total Norwegian population as reference rates. The association between CHD and risk of cerebrovascular disease was analyzed by including CHD as

a time-dependent covariate in a Cox regression, reported as hazard ratios (HRs) with 95% CIs. Further details are provided in Methods in the online-only data supplement.

Results

In total, 3144 persons with FH (46.6% men, mean (standard deviation (SD)) age at inclusion was 39.9 years (14.9)) were included in analyses of cerebrovascular disease and compared to the age, sex and calendar year adjusted Norwegian population. The analyses of ischemic stroke included 3166 persons with FH (46.5% men, mean (SD) age at inclusion 39.2 years (14.3)). Total follow-up was more than 18 500 person years.

A total of 46 cases of cerebrovascular disease were observed in persons with FH, 19 women and 27 men, and no significant increased risk of cerebrovascular disease was found (Table 1). When ischemic strokes were analyzed, 26 ischemic strokes were observed (9 women and 17 men), and again, no significant increased risk in persons with FH (Table 1).

In the group of 46 patients with cerebrovascular disease, 23 (50%) had previous CHD, 11 women (57.9%) and 12 men (44.4%). In Cox regression analyses of the association between CHD and cerebrovascular disease we found a significant interaction between sex and CHD ($p_{interaction}$=0.04). In separate analyses for men and women, a significant association between previous CHD and risk of cerebrovascular disease was found in women (HR=3.29, 95% CI (1.20-9.00)) but not in men (HR=1.03, 95% CI (0.45-2.37)).

Discussion

In our cohort of 3170 genetically verified persons with FH and more than 18 500 person-years of follow-up, there was no increased incidence of cerebrovascular disease or ischemic stroke compared to the entire population of Norway, and as far as we know, this is the largest data set to date investigating this. Acknowledging the contribution of age to the risk of cerebrovascular disease, mean age at inclusion was relatively low in the our cohort.

The finding of no increased risk of cerebrovascular disease and ischemic stroke in persons with high LDL-cholesterol from birth is interesting, and challenges the concept of LDL-cholesterol being a major risk factor for cerebrovascular disease and ischemic stroke. Importantly, in the present cohort, the risk of CHD was more than fourfold increased during the same period of time.[6] A Mendelian randomization study recently found that persons with lifelong low levels of PCSK9 and LDL-cholesterol had lower risk of CHD, but with no effect on ischemic stroke.[10] This has questioned the relation between LDL-cholesterol and ischemic strokes. Indeed, much of the support for the LDL-cholesterol hypothesis regarding risk of ischemic stroke is based upon the reduced incidence of stroke found in landmark statin trials.[11] However, the largest published meta-analysis of statin trials found only a small reduction in stroke risk among statin-treated men, and no effect on stroke incidence in women.[11]

The results of most previous studies on cerebrovascular disease and stroke in persons with FH are in agreement of our findings.[9,12,13] In contrast, Toell et al recently demonstrated increased prevalence of ischemic strokes and transient ischemic attacks in persons with FH,[8] however, with FH defined by clinical criteria and not genetic criteria.

Previous hospitalization for CHD increased the risk of cerebrovascular disease in women in the present study but surprisingly not in men, this finding warrants further investigation as the sample is quite small.

Limitations

Registration of actual lipid levels and medication, was not possible in the present study, and should be addressed in future studies of stroke in persons with FH. Given the registry-based study design, we did not have information on lifestyle factors. Selection bias is always an important issue in register studies. Importantly, all physicians in Norway may request genetic testing of FH free of charge, reducing the risk of bias due to economy.

Conclusions

In this large cohort of 3170 genetically verified persons with FH, with more than 18 500 person-years of follow-up, risks of cerebrovascular disease and ischemic stroke were not increased compared to the age, sex and calendar year adjusted Norwegian population, despite the previously reported higher risk of CHD in this cohort. Our results raise new questions regarding the specific role of LDL-cholesterol in cerebrovascular disease and ischemic stroke.

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Table 1. Standardized incidence ratios (SIRs) for cerebrovascular disease and ischemic strokes in persons with familial hypercholesterolemia.

Disease	Gender	Incident cases	Person years in 1000	Crude incidence rate per 1000 person years (95% CI)	Expected number of cases	SIR (95% CI)*
Cerebrovascular disease (N=3144)						
	Women	19	9.7	2.0 (1.2-3.1)	21.6	0.9 (0.6-1.4)
	Men	27	8.5	3.2 (2.2-4.6)	23.2	1.2 (0.8-1.7)
	Total	46	18.3	2.5 (1.9-3.4)	44.8	1.0 (0.8-1.4)
Ischemic stroke (N=3166)						
	Women	9	9.8	0.9 (0.5-1.8)	12.1	0.8 (0.4-1.5)
	Men	17	8.6	2.0 (1.2-3.2)	13.6	1.3 (0.8-2.1)
	Total	26	18.4	1.4 (1.0-2.1)	25.1	1.0 (0.7-1.5)

* SIR=Standardized incidence ratio obtained using indirect standardization. CI=Confidence interval.