Risk of Ischemic Stroke and Total Cerebrovascular Disease in Familial Hypercholesterolemia

A Register Study From Norway

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Background and Purpose—Familial hypercholesterolemia (FH) is a common autosomal dominant disease leading to increased level of serum LDL (low-density lipoprotein) cholesterol and risk of coronary heart disease. 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 people with genetically verified FH compared with the entire Norwegian population and examined whether people in this cohort with previous cohort had increased risk of cerebrovascular disease.

Methods—Incidence rates of hospitalization for cerebrovascular disease (among 3144 people with FH) and ischemic stroke (among 3166 people with FH) were estimated by linkage of FH people to Cardiovascular Disease in Norway—a nationwide database of cardiovascular disease hospitalizations (2001–2009). We calculated standardized incidence ratios and used Cox regression to estimate hazard ratios.

Results—A total of 46 cases (19 women and 27 men) of cerebrovascular disease were observed in the cohort of people with FH, with no increased risk of cerebrovascular disease compared with the general population (standardized incidence ratio, 1.0; 95% CI, 0.8–1.4). Total number of ischemic strokes in the cohort of people with FH was 26 (9 women and 17 men), with no increased risk compared with the general population (standardized incidence ratio, 1.0; 95% CI, 0.7–1.5). Prior coronary heart disease significantly increased cerebrovascular disease risk in women (hazard ratio, 3.29; 95% CI, 1.20–9.00) but not in men (hazard ratio, 1.03; 95% CI, 0.45–2.37; $P_{\text{interaction}}$=0.04).

Conclusions—In a large cohort of genetically verified FH, risks of cerebrovascular disease and ischemic stroke were not increased compared with the total Norwegian population. **(*Stroke*. 2019;50:172-174. DOI: 10.1161/STROKEAHA.118.023456.)**

Key Words: cerebrovascular disorders ■ cholesterol, LDL ■ hyperlipoproteinemia type II ■ risk ■ stroke

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, LDL (low-density lipoprotein) cholesterol-lowering therapy is important in both primary and secondary prevention of cerebrovascular diseases, including stroke.[3]

People 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 because of the increased LDL cholesterol load.[5–7] With the increased risk of atherosclerosis, the risk of stroke in patients with FH is expected to be high. However, whether the risk of stroke in patients with FH 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 people 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.

Methods

The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway, and is a cohort study of people with FH identified from the Unit for Cardiac and

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Cardiovascular Genetics Registry linked to the Norwegian Cause of Death Registry and the Cardiovascular Disease in Norway 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 Unit for Cardiac and Cardiovascular Genetics Registry after written informed consent. Before 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 7 years. Patients were followed from inclusion in the FH registry until the first occurrence of cerebrovascular disease, death, or December 31, 2009, whichever came first. Incident events of ischemic stroke were defined in the same manner. We calculated incidence rates and standardized incidence ratios (with 95% 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 with 95% CIs. Further details are provided in Methods in the online-only Data Supplement.

Results

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

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

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 (hazard ratio, 3.29; 95% CI, 1.20–9.00) but not in men (hazard ratio, 1.03; 95% CI, 0.45–2.37).

Discussion

In our cohort of 3170 genetically verified people with FH and >18 500 person-years of follow-up, there was no increased incidence of cerebrovascular disease or ischemic stroke compared with 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 our cohort.

The finding of no increased risk of cerebrovascular disease and ischemic stroke in people 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 >4-fold increased during the same period of time.[6] A Mendelian randomization study recently found that people with lifelong low levels of PCSK9 (proprotein convertase subtilisin/kexin type 9) 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 about the risk of ischemic stroke is based on 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 people with FH are in agreement of our findings.[9,12,13] In contrast, Toell et al[8] recently demonstrated increased prevalence of ischemic strokes and transient ischemic attacks in people with FH, 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 because the sample is small.

Table. SIRs for Cerebrovascular Disease and Ischemic Strokes in People With Familial Hypercholesterolemia

Disease	Sex	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 indicates standardized incidence ratio.
*SIR obtained using indirect standardization.

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 people 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 because of economy.

Conclusions

In this large cohort of 3170 genetically verified people with FH, with >18 500 person-years of follow-up, risks of cerebrovascular disease and ischemic stroke were not increased compared with 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 on the specific role of LDL cholesterol in cerebrovascular disease and ischemic stroke.

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