Prognosis in Familial Atrial Fibrillation
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Atrial fibrillation (AF) is a common arrhythmia associated with substantial morbidity and a markedly increased risk of ischemic stroke. It accounts for one third of all strokes in patients above the age of 65 and is also associated with an increased mortality. In recent years, risk models for AF prediction have been developed based on clinical and demographic variables. AF may also present as familial disorder. Several studies have shown an association of genetic variants with AF and indicated that familial AF increases the risk of AF. Considering the high and increasing number of AF patients in daily practice, the clinician is interested in the clinical course of these familial forms of AF and whether familial AF patients would benefit from a different management strategy than other AF patients.

Heterogeneity of both genetic background and clinical manifestations in familial AF remains largely uncharacterized. Concomitant rhythm disorders, as well as cardiomyopathies, are common in patients with familial AF. A positive family history for AF in an apparently lone AF patient may be a marker for wider spectrum of cardiac pathologies, and one first message is that this should be investigated when the cardiologist identifies a patient with familial AF.

Although studies have identified several genetic loci associated with AF, it is still unclear whether genetic profiling can identify AF patients at greatest risk of cardiac events or cardioembolic stroke. One might speculate that a patient with familial AF will have earlier onset of AF and overall longer duration of AF, which might affect the risk of stroke (although this is not clearly demonstrated in other AF patients). An earlier onset and longer duration of AF might also promote a so-called cardiomyopathy in some patients, which may worsen prognosis. In the analysis of a nation-wide cohort study about familial AF in Denmark, Gundlund et al found that age difference was indeed evident with a median age at AF diagnosis of the familial AF patients of 50 years in comparison to the nonfamilial AF patients who had a median age at AF diagnosis of 77 years. However, the researchers found that long-term risks for death and thromboembolic complications were similar in familial and nonfamilial AF patients. The researchers have to be congratulated given that their data set is quite unique. It has the major advantage of being nationwide, thus theoretically avoiding selection biases commonly observed in many works on these issues. Some clinical characteristics are missing and more granular data would be of interest, but the multivariable analyses seem quite robust and they are unlikely to be reproduced easily in many other cohorts. After matching the cases and the controls in a 1:1 match upon age at AF diagnosis, year at AF diagnosis, and sex, there were statistically more prevalent diabetes mellitus, coronary artery disease, and vascular disease in nonfamilial AF, but the absolute differences were relatively minimal. Importantly, matching resulted in very similar CHA2DS2-VASc scores, which was a key determinant for an unbiased analysis of the risk of stroke associated with familial AF per se. The lack of differences in the long-term risk of thromboembolic complications between familial and nonfamilial indicates that the perceived possible different effect of familial pattern against the risk of death and thromboembolic events seems irrelevant in AF patients when using a contemporary risk stratification scheme, the CHA2DS2-VASc score. As a result, this would suggest a similar antithrombotic treatment approach for familial AF patients as for the general AF population.

These results are complementary to those recently published by Lubitz et al. Using genome-wide data from an independent large-scale analysis of common variants known to be associated with AF, they found that AF genetic risk was associated with AF and cardioembolic stroke in 18,919 individuals. Nevertheless, given that genetic information improved prediction minimally and afforded small improvements in discrimination of AF risk, the researchers concluded that widespread use of genetic risk profiling does not need to be incorporated into routine clinical decision making.

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However, familial AF may help to identify the etiology for strokes, more likely to be caused by thromboembolism from AF. This would help decision making in patients with cryptogenic stroke or, at the other end of the spectrum, for the many patients with several putative etiologies after ischemic stroke. Beyond the relatively wide aspect of familial AF, there may be a heritable component underlying ischemic stroke. AF-associated genetic variants on chromosomes 4q25 and 16q22 have been associated with cardioembolic strokes. An AF genetic risk score has been reported for and 16q22 have been associated with cardioembolic stroke. AF-associated genetic variants on chromosomes 4q25 AF, there may be a heritable component underlying ischemic stroke. Beyond the relatively wide aspect of familial AF. This would help decision making in patients with cryptogenic stroke or, at the other end of the spectrum, for patients with several putative etiologies after ischemic stroke. More likely to be caused by thromboembolism from AF. Considering the more specific subgroup of patients with so called lone AF, Jurkko et al found that familial AF may account for 20% of the patients, and they were able to show that the arrhythmia triggers for lone AF were heterogeneous (premature atrial contractions, vagal or sympathetic related), but were often family specific. Overall, it seems that associated rhythm disorders, as well as cardiomyopathies, are not uncommon in patients with familial AF. A family history for AF may be the indicator of a variety of cardiac pathologies, which may actually be the main determinant of prognosis. An element to be taken into account (and a possible bias) that is families with long life expectancy for any reason may be at higher risk for familial AF attributed to older age of relatives. Other researchers defined familial AF as premature when the first detected occurrence is at age 65 years or younger in a first-degree relative. Similarly, Oyen et al performed their analysis in patients with lone AF before age 60 years. Consequently, the researchers performed a sensitivity analysis in which familial AF was restricted to patients with a first-degree family member diagnosed with AF before the age of 70 years. Whereas this conservative approach should decrease the bias selecting patient with a longer life expectancy, the researchers actually found a lower risk of death in this subgroup of patients with familial AF. Maybe the study in 4329 cases still lacks some power for definite conclusions and the researchers acknowledge this point, but a 17% lower risk of death has to be considered beyond statistical significance. This is a quite intriguing result, which is uneasy to explain at this stage. Maybe a better awareness about AF may lead to an earlier and holistic management in patients with familial AF. This would be an interesting part of a general strategy of AF screening in the population, advocating that an early detection and treatment of patients with asymptomatic AF before the first complications occur is a recognized priority for the prevention of cardiovascular events.

Disclosures

Fauchier reports consulting and/or lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, and Novartis. Clementy reports consulting and/or lecture fees from Medtronic. Bisson reports no COI.

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