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Genetic diagnosis of individuals at risk of CADASIL: prospect for future therapeutic development

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Abstract
CADASIL is the most frequent hereditary cerebral small vessel disease worldwide. The disease is responsible for a slow and progressive accumulation of cerebral ischemic insults that lead to disabling cognitive and motor symptoms at late age. Although there is currently no cure for this condition, future therapies may concern subjects only at early stage of the disease. This will raise the question of the participation of asymptomatic carriers of pathogenic NOTCH3 gene mutation in future clinical trials, which will presuppose acceptance of presymptomatic genetic diagnosis. In this study, we questioned the population at risk of CADASIL who had not undergone a diagnostic procedure yet. Based on a questionnaire survey carried out by an independent team of sociologists, we analyzed what underlies the choice of people at risk to undergo or not to undergo a genetic test, and what could constitute the tipping point that could lead people who were initially not interested in their diagnosis to have recourse to it. Our results suggest that, far from being a simple, unequivocal path, the decision-making process leading to the choice of diagnosis is initially slowed down by the need to distance oneself from the disease so that it doesn't take over one's life, and then evolves under the influence of a complex tangle between advancing age, the presence of early symptoms, and the personal relationship with uncertainty. It cannot be ruled out that the real and imminent prospect of therapy may also modify responses to this type of survey.

Keywords Presymptomatic diagnosis · Genetic testing · CADASIL · Decision making · At-risk population · Family disease · Clinical Trial

Introduction

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is the most frequent monogenic cerebral small vessel disease [4, 35]. It is caused by stereotyped cysteine-altering variants in the NOTCH3 gene encoding a receptor at the surface of smooth muscle cells and pericytes within the wall of microvessels [20, 25, 26]. The disease is inherited following an autosomal dominant pattern of transmission [3]. In its classical form, as initially reported in presence of mutations located in EGFr domains 1–6, CADASIL appears to have a complete penetrance. This means that any offspring of an individual having the mutated gene has a 50% risk of carrying the responsible mutated gene and therefore developing, more or less late, but with certainty, the symptoms of the disease [3]. It is also an adult-onset disease whose first manifestations, as migraine with aura, may appear when young, around 20 and 40 years of age. Conversely, the most disabling manifestations, resulting from the accumulation of focal cerebral ischemic lesions as gradual cognitive decline or motor deficit usually occur much later, often after the age of 50 years and can even develop in some individuals during old age [4, 5].

To date, there is no preventive or curative treatment for this severe condition [12]. In France, as in other European countries [30], the presymptomatic diagnosis of at-risk individuals is based on a step-by-step procedure inspired by that recommended in Huntington's disease, a late-onset hereditary neurodegenerative disorder [9]. Specialized

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consultations with a geneticist, neurologist and psychologist are usually offered, and a minimum delay is required before any final decision is taken on whether or not to proceed with the genetic test [30]. In this way, each person has the opportunity to reflect on what knowing their genetic status could mean for them and on the potential impact of a diagnosis on everyday life in the absence of treatment and personalized prognostic evaluation. In France, where this policy was adopted since the first genetic tests in CADASIL, the demand for presymptomatic diagnostic tests has remained limited to date [30]. Moreover, only one third of individuals who consulted with the intention of undergoing a presymptomatic diagnosis actually went through the entire procedure [30]. This is in line with studies of presymptomatic genetic testing in other severe and late neurologic conditions [13, 14, 36]. Different information have been already collected concerning such population at risk, particularly, their socioeconomic characteristics, their variable family contexts as well as their motivations and expectations regarding the early diagnosis of a late-onset and disabling genetic disease. A key result is that not only a limited proportion of individuals at risk actually undergo genetic testing [9, 13, 14, 19, 36] but also that this population is more likely to turn to genetic testing when a treatment is available [22, 23, 27]. The motivations of people at risk of conditions as Huntington's disease who consulted for potential genetic testing [7, 18, 31], who ultimately underwent the genetic screening [7, 22, 29] or who chose not to obtain genetic testing [6], have been previously analyzed as well as the propensity of mutation gene carriers to recommend or not to be tested to their relatives [28]. Different methods as file reviews, questionnaires, interviews, surveys were previously used. However, due to the predominantly hospital-based recruitment of individuals who already demonstrated their interest in presymptomatic diagnosis to medical teams, many of these studies were necessarily biased. More specifically, people who decided from the outset not to seek such a genetic diagnosis were by nature excluded. Studies without such limitation are therefore scarce. For Huntington's disease, interviews focused on the experience of growing up in an affected family has been already obtained in 33 individuals at risk who were recruited based on snowballing from contacts at the Norwegian National Association for the disease and via websites and social media [33]. In a different study focusing on the intra-family transmission of information in a context of low uptake of testing for Huntington's disease, the recruitment was based both on the file of subjects who previously attended an expert consultation and on calls via websites of patients' associations [28].

In CADASIL, the potential development of future clinical trials will obviously raise concerns about the adequacy of the current presymptomatic diagnostic approaches. Accumulating data support that future preventive treatment should be administered in CADASIL patients long before the accumulation of cerebral infarcts and before the final resulting loss of smooth muscle cells in the vascular wall [12]. Presymptomatic CADASIL patients could therefore become potentially eligible for these trials in future if they agree to take the step of undergoing genetic testing. Clinical trials could thus involve not only CADASIL patients who have already undergone the presymptomatic diagnosis procedure but also individuals at risk who have already considered genetic testing but had decided not to do so, and those who had not yet sought to perform a genetic diagnosis.

In the present study, we aimed to explore the reasons for the initial choices made among subjects at-risk of CADASIL, but also of the tipping point that could lead people initially uninterested in diagnosis to finally resort to it, including the potential issues related to the participation in a clinical trial. For this purpose, we carried out a large-scale survey based on a broadly recruited sample of individuals to minimize obvious potential selection biases.

Methods

This survey is part of a series of investigations developed by a group of sociologists (MA, VR, and FP) whose general aim was to gain, independently of clinicians and researchers, a better understanding of the difficulties, needs and expectations of patients and families affected by the disease. One of specific objectives was to report the key issues raised by: (1) people who had already been diagnosed; (2) their close relatives who were not directly concerned by the disease and (3) subjects at risk who belonged to an affected family but who did not know their genetic status. Before preparing the questionnaires for each of these different groups, a qualitative interview of 30 volunteer individuals had been performed which included 18 carriers of a cysteine-altering NOTCH3 variant responsible for the disease, eight relatives who were not at-risk for CADASIL and four asymptomatic subjects who were at risk of being affected. This enabled to gather the experience of different family members from various perspectives. The results allowed identifying the most relevant themes for preparing a first version of the questionnaire surveys for patients with confirmed diagnosis, for their relatives and for at-risk subjects. These first questionnaires were thereafter discussed and amended with the help of the board of CADASIL France, the French Association of people affected by CADASIL and their families. They were subsequently finalized after additional recommendations obtained from the medical staff of the National Reference Centre for the disease (CERVCO, http://www.cervco.fr).

Thereafter, the final version of these questionnaires was widely distributed, with an online version made available on both the national referral centre and association websites as well as using multiple mailings by regular mail or electronic

emails. More specifically, a paper copy was sent to all patients who previously consulted the referral centre CERVCO in the past ($n=430$) and to all identified members of the association CADASIL France without any known email address ($n=190$). An email was sent to all the other members of the association CADASIL France ($n=263$). Finally, a link to upload the online version of the questionnaire was posted on the website of the association CADASIL France and on that of the referral centre, along with a short explanatory comment. Moreover, people who had received the paper questionnaire had also the option of responding directly online.

Each questionnaire comprised about 40 questions which covered the following aspects, in addition to the basic socio-demographic data: (1) experience of the diagnostic pathway; (2) exact reasons for seeking diagnosis or for delaying diagnosis (at-risk individuals); (3) sources of information about the disease; (4) main issues discussed concerning the disease; (5) resources considered most important in relation to the disease, (6) current and future concerns (for carriers and their families); (7) position regarding future clinical trials. The questionnaires were carried out in such a way as to preserve the complete anonymity of respondents. For this reason, the age of individuals was specified in 10-year categories, and neither their date of birth, nor their name or initials were collected.

This study analyzes data from both the at-risk and diagnosed populations to provide a comparative approach and further insight into the interpretation of the data. Descriptive statistics (frequencies, mean and median values, inter-quartile ranges (IQR), standard deviation and range values) were used to describe the results obtained in the different groups. Comparisons were performed using the χ^2 test or the Student's t tests and multivariate analysis was performed using logistic regression analysis when needed. p values of less than 0.05 were considered statistically significant.

The questionnaire survey and its protocol of administration was approved by the Ethics Institutional Review Board (IRB00003888, IORG0003254, FWA00005831) of the French Institute of Medical Research and Health. The study was, conducted as part of research project granted by the Agence Nationale de la Recherche (ANR) RHU- TRT-cSVD (opinion number 18-485-bis from July 7, 2020).

Results

Population of respondents

From 883 online and paper questionnaires sent by email or by post, 359 replied questionnaires were collected during the study period. Fifteen returned partially completed. These questionnaires were from 197 NOTCH3-mutation carriers, 81 close relatives and 81 individuals "at risk" of the disease (whose one of the parent was already concerned by the disease). The responses of the relatives were not analyzed in this study. The main characteristics of the other respondents are presented in Table 1. Overall, twice as many women as men responded to the survey. The population of mutation carriers with a family history of the disease did not differ from those without a positive family history in terms of sex, family status, parenthood or occupational categories (all p values >0.5). Individuals at risk who had already consulted a physician about CADASIL did not differ from those also at risk who had never consulted (all p values >0.5, see Table 1).

At risk individuals who responded to the questionnaire were younger ($p<0.0001$) and had less frequently children ($p=0.0003$) than already diagnosed individuals. They did not differ from the latter regarding their family status or occupational activities (Table 1).

Current sources of information in the different populations of respondents

Among the respondents, the main external sources of information related to CADASIL were concentrated on three French websites: (1) the website of the National Referral Centre CERVCO, (2) the Orphanet website, a portal and information server dedicated to all rare diseases and orphan drugs; (3) the website of the CADASIL France patients association. The CADASIL France website is the most consulted by both groups. Among the respondents, a larger proportion of mutation carriers had already consulted the Referral Centre website ($p=0.0004$, see Table 2) and the Orphanet website ($p=0.0005$), or any of these two medical websites ($p=0.0011$). Interestingly, 25% of mutation carriers and 20% of people at risk had never consulted any of the three sites dedicated to the disease in France (Table 2).

Current circumstances surrounding the genetic diagnosis when a family history had been already established

In the population of respondents, individuals who were aware of a family history of the disease presented with different behaviors in relation to their genetic diagnosis. The variable time from awareness of a disease risk in the family up to the genetic diagnostic test is presented on Fig. 1. The results show a U shape. A large group of individuals had a relatively rapid confirmation of their diagnosis after they learned that the disease was present in their family, while, on the other hand, another large proportion of individuals awaited up to a decade prior the genetic confirmation of their disease. The age of genetic testing did not differ between those who were diagnosed within three years of becoming

Table 1 Description of the population of respondents

	Mutation carriers				At risk persons				
	Family history = no	Family history = yes	*p* value	Total	Consultation = yes	Consultation = no	*p* value	Total	*p* value
N[a]	81	114		197	29	52		**81**	
Sex									
Women	57 (72%)	76 (67%)	0.5	134 (69%)	25 (86%)	37 (73%)	0.22	62 (77.5%)	0.09
Men	24 (28%)	38 (33%)		62 (31%)	4 (14%)	14 (27%)		18 (22.5%)	
Age Categories									
20–29	**0%**	**1%**	**0.012**	**1%**	10%	10%	0.21	**10%**	**< 0.0001**
30–39	**5%**	**12%**		**8%**	17%	19%		**18%**	
40–49	**14%**	**35%**		**26%**	41%	23%		**30%**	
50–59	**30%**	**21%**		**25%**	11%	25%		**19%**	
60–69	**35%**	**21%**		**26%**	17%	9%		**12%**	
70–79 years	**15%**	**10%**		**12%**	4%	4%		**3%**	
Family status									
In couple	56 (69%)	68 (60%)	0.25	126 (64%)	15 (52%)	30 (59%)	0.66	45 (56%)	0.18
Alone	19 (23%)	29 (26%)		48 (24%)	8 (28%)	10 (20%)		18 (23%)	
With other family members	6 (7%)	16 (14%)		22 (11%)	6 (22%)	11 (22%)		17 (21%)	
With other people		1 (1%)		1 (1%)		1 (2%)		1 (1%)	
Parenthood									
Yes [aged over 40 years]	68 (84%)	96 (84%)	0.98	**166 (84%) [86%]**	19 (66%)	33 (63%)	0.85	**52 (64%) [73%]**	**0.0003**
No	13 (16%)	18 (16%)		**31 (16%)**	10 (34%)	19 (37%)		**29 (36%)**	
Contact with a diagnosed family member before diagnosis									
Yes	**16 (21%)**	**104 (91%)**	**< 0.0001**	**121 (62%)**	26 (93%)	45 (90%)	0.58	**71 (91%)**	**< 0.0001**
No	**65 (78%)**	**10 (9%)**		**75 (38%)**	2 (7%)	5 (10%)		**7 (9%)**	
Occupation (before retirement)									
Farmers and manual workers	6 (8%)	7 (6%)	0.92	13 (7%)	1 (4%)[a]	2 (4%)	0.17	3 (4%)	0.67
Employees	28 (35%)	35 (32%)		63 (33%)	14 (48%)	13 (26%)		26 (34%)	
Intermediate professions	8 (10%)	13 (12%)		21 (11%)	2 (7%)	8 (16%)		10 (13%)	
Executives and higher intellectual professions	25 (31%)	38 (34%)		63 (33%)	9 (33%)	15 (30%)		24 (31%)	
Craftsmen, shopkeepers and company managers	5 (7%)	12 (11%)		17 (9%)	0(0%)	5 (10%)		5 (6%)	
No professional activity	7 (9%)	6 (5%)		13 (7%)	2 (7%)	7 (14%)		9 (12%)	

Bold values indicate the statistically significant differences

[a]A slight discrepancy in the total numbers may result from the absence of a single response in few individuals who took part in the study

Table 2 Main sources of information among the respondents of the survey

Respondents seeking information	Mutation carriers ($N=197$)	People at risk ($N=81$)	p value
Referral centre website	113 (57%)	30 (37%)	0.0004
Orphanet website	82 (42%)	21 (26%)	0.0005
CADASIL France Association website	127 (64%)	61 (75%)	0.3834
Any of the medical websites	127(64%)	35 (43%)	0.0011
Number of websites visited			
3 websites (all)	68 (35%)	15 (19%)	
2 websites	39 (20%)	17 (21%)	0.00173
1 websites	40 (20%)	33 (41%)	
None of the 3 websites	50 (25%)	16 (20%)	

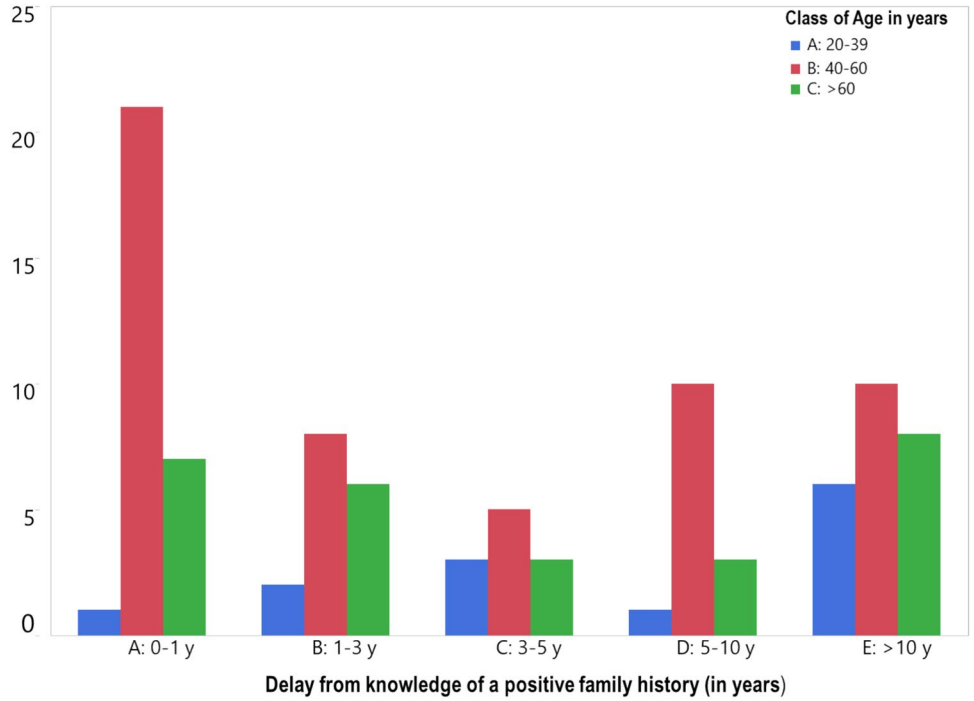

Fig. 1 Time from awareness of disease risk to actual date of diagnosis

Table 3 Symptoms related to CADASIL in NOTCH3-mtation carriers according to their awareness of the disease risk in the family

Mutation carriers symptoms	Diagnosis < 3 years after knowledge of family history	Diagnosis > 3 years after knowledge of family history	p value
N	45	49	
Age			
30–39 years	3 (7%)	10 20%)	0.11
40–49 years	17 (38%)	16 (33%)	
50–59 years	12 (27%)	9 (18%)	
60–69 years	6 (13%)	11 (22%)	
70–79 years	7 (15%)	3 (6%)	
No related symptoms	9 (20%)	13 (27%)	
Related but non-disabling symptoms	17 (39%)	29 (59%)	
Related-disabling symptoms	18 (41%)	7 (14%)	0.0146

aware of a family risk and those who waited longer to be diagnosed ($p = 0.11$, Table 3). The individuals diagnosed early after they became aware of the disease in the family presented nearly 3 times more frequently disabling clinical manifestations than those diagnosed later (Table 3).

Position of individuals at risk regarding the genetic diagnostic test

Among the 81 individuals at risk who participated to the survey (62 women and 18 men), two subjects (2.5%) had decided to undergo the genetic testing, 40 (50%) not to undergo this procedure, the others did not make any decision yet ($n = 32$) or did not want to answer ($n = 7$). The proportion of people at risk who had decided not to have a genetic test at the time of the study tended to decrease according to age ($p = 0.2$, Fig. 2). About half (36/74) of the individuals at risk already experienced symptoms possibly related to CADASIL; 40% (32/74) chose not to undergo the genetic testing and 56% (39/81) did not make any decision or did not want to answer. In the at-risk population, the decisions to request genetic testing, not to request genetic testing, or not to decide did not differ in the presence or absence of disease symptoms (Table 4), nor according to sex (p values between 0.2 and 0.9, data not shown). A third of the respondents had consulted a specialist. The decision not to undergo genetic testing, or the lack of a decision, was not linked to whether or not the individual at risk had seen a specialist beforehand (Table 4).

Factors that could potentially influence a decision to carry out genetic testing in individuals at risk

We asked the respondents "at risk" to indicate among different motives the reasons that would lead them to decide to undergo genetic testing in future (onset of mild symptoms, onset of severe symptoms, illness of a relative, personal parental project, pressure from relatives or prospect of a therapeutic trial). The results are summarized in Table 5. The onset of symptoms was the first response cited in two third of individuals (either mild or severe symptoms). Next, about two out of five individuals indicated that the prospect

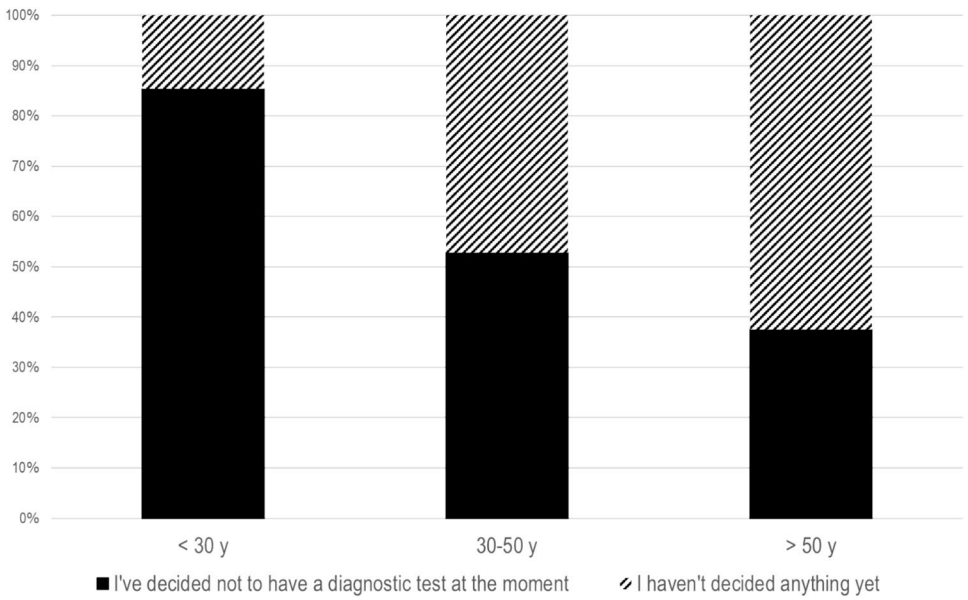

Fig. 2 Age and position in relation to the diagnostic test

Table 4 Disease symptoms and consultations of a specialist in individuals at risk

	No disease symptoms	Disease symptoms	*p* value	Did not consult a specialist	Already consulted a specialist	*p* value
N	38	36		48	23	
I have decided not to undergo genetic testing for the moment ($N = 40$)	24 (64%)	16 (44%)	0.09	27 (56%)	13 (56%)	0.9
I haven't decided anything yet ($N = 32$)	14 (36%)	18 (50%)		21 (44%)	10 (44%)	
I have decided to undergo genetic testing ($N = 2$)	0%	2 (6%)		0	0	

Seven individuals who did not want to answer were not considered in this table

Table 5 Incentives for people at risk to undergo genetic diagnosis and considerations that would keep them from this procedure

	Yes	No
Which of the following would lead you to undergo genetic testing?		
The onset of symptoms	**52 (65%)**	29 (35%)
A parental project among respondents < 50 years	9 (19%)	**39 (81%)**
A parental project among respondents < 50 years with no children	8 (40%)	**12 (60%)**
The prospect of a clinical trial (for drugs)	30 (37%)	**51 (63%)**
The illness of a relative	27 (33%)	**54 (67%)**
Pressure from relatives	4 (5%)	**77 (95%)**
Which of the following would keep you from undergoing genetic testing?		
Fear that the disease may become too invasive in the life	**46 (57%)**	35 (43%)
Consequences on the professional activity	18 (22%)	**63 (78%)**
Consequences on social relationships	16 (20%)	**65 (80%)**
A real estate project	13 (16%)	**68 (74%)**
Pressure from family and friends	3 (4%)	**78 (96%)**
A parental project (all individuals)	1 (1%)	**80 (99%)**

Bold valuse indicates the statistically significant

of a clinical trial or a parental project, for the youngest subjects, could also lead them to undergo genetic testing. The illness of a relative or any pressure from a relative appeared finally the weakiest incentive motives. Conversely, by far, the most important reason for people at risk not to seek a diagnosis was the fear that the disease could become too intrusive in their daily lives (57%). This was felt well before any consideration given to professional, social, or familial (estate) projects. These different proportions were similar in men and women (data not shown, p values between 0.3 and 0.9).

Position of individuals at risk regarding their participation to future clinical trials and their potential impact on genetic diagnosis

The responses of people at risk regarding clinical trials were similar to those of NOTCH3-mutation carriers and were characterized by a high proportion of people expressing their willingness to participate in such a trial (73%, compared to 87% for mutation carriers). However, in almost half of these cases, such a decision would depend upon a potential risk of side effects from the drug being tested (Table 6). There was a discrepancy between the high proportion of individuals at risk willing to participate in a trial of a preventive treatment for their disease (73%) and the smaller proportion (37%) of individuals in the same group who would undergo genetic testing in the prospect of a therapeutic trial in general (Tables 5, 6).

Discussion

This study is the largest survey ever carried out into the question of genetic diagnosis and focused on individuals at risk in families affected by CADASIL. As expected in this type of studies, the highest socio professional categories were over-represented both in already diagnosed and

Table 6 Main reasons for taking part in a therapeutic trial, and, where appropriate, carrying out a genetic test for a potential individual inclusion

	Mutation carriers	Individuals at risk	*p* value
N	192	67	
Questions: Would you be willing…	to participate in a clinical trial for testing a drug that could prevent disease progression ?	to undergo genetic testing to participate in a clinical trial for testing a drug that could prevent disease progression ?	
Answers			
Yes	108 (56%)	31 (46%)	0.08
Yes but depends on the risk of side effects	58 (30%)	16 (24%)	
Yes but depends on the length of the trial	2 (1%)	2 (3%)	
No	9 (5%)	5 (7%)	
I don't know	15 (8%)	13 (19%)	

in at-risk individuals. However, neither the occupational activity nor the family structure differed between these two groups. Moreover, the results show that more than 9 out of 10 people, whether diagnosed or not, had first-hand experience of the disease through close contact with a patient suffering from the condition. Altogether, these findings support that a greater or lesser proximity to the disease, the socio-economic situation or even, the family structure, would not play a major role in the decision of being genetically diagnosed or not. Conversely, age might well represent a key factor in the decision. The respondents who had already undergone genetic testing were the oldest, which is consistent with the fact that they were most often already diagnosed after the onset of suggestive symptoms at a median age of over 60 years [11, 37]. As expected, on the other hand, individuals at risk were the youngest respondents and were therefore, more likely to be childless. An interesting finding is however that among respondents younger than 40 years, those who have children are more likely to have been diagnosed than those without children. Thus parenthood is apparently linked to a higher propensity to get diagnosed. Our qualitative survey nevertheless suggests that this trend is not related to the use of prenatal diagnosis or medically assisted reproduction.

Our study also shows that individuals at risk were relatively well informed about CADASIL. A vast majority of them had already searched the Internet for detailed information about this condition.More than 80% had already consulted at least one of the three websites dedicated to this topic in France, and 21% had already searched for information on all three of these sites. This is only slightly less than the proportion of patients who have already been diagnosed. They differed from subjects who had already been diagnosed in that they were significantly less likely to consult websites managed by medical or expert teams, while an equivalent proportion had consulted the family reference site available in France. However, these findings might be the consequence of our recruitment strategy: it is likely that most at-risk people accessed the questionnaire through CADASIL France website. These results also suggest that patients whose diagnosis has already been confirmed may search for more information about the disease, and/or that individuals at risk may want to keep a certain distance from the medical world.

Overall, the proportion of individuals with suggestive clinical manifestations of the disease was high-more than 70%—among those who already had undergone genetic testing. Interestingly, we observed that patients who had been diagnosed less than 3 years after they became aware of a confirmed diagnosis in their family presented more often suggestive symptoms of the disease, either mild or severe, than individuals who were diagnosed later. Their age did not differ from patients waiting longer for genetic diagnosis. In parallel, among people at risk of CADASIL who had not yet undergone diagnostic testing, both the two subjects who had planned to be tested already experienced possible disease symptoms Among at-risk individuals who had not made a decision at the time of this study, the onset of symptoms was considered by far the main reason which could lead in future to get genetic testing. These results strongly suggest that the perception of symptoms may ultimately represent a key element in the general decision to undergo a genetic diagnostic test, even in at-risk individuals who are still considered not to be ill. These results are in line with data obtained in the diagnostic context of Huntington's disease. Subjects with few disease symptoms are three times less likely to abandon the step-by-step diagnostic procedure than individuals without any symptom of Huntington's disease [29]. Moreover, 91% of people at risk of the condition who thought they had symptoms turned out to be carriers of the disease gene. Our results and these earlier data therefore suggest that the term 'pre-symptomatic' for genetic testing in some at risk individuals may ultimately be somewhat misleading, both with regard to CADASIL and Huntington's disease. As our survey showed that individuals at risk were fairly-well informed, particularly via the Internet, it cannot be ruled out that their decision to undergo a genetic diagnosis is influenced by the appearance of symptoms, even very subtle.

In the at-risk group, half of the respondents (49%) stated that they had decided not to be tested at time of the survey, while 38% reported that they had not yet made a decision. Such results could be interpreted according to Cox et al. [7] with analyzing both the 'meaning and experience of the decision' to order a predictive genetic test. This approach is at odds with the "why" question, which asks why people make decisions rather than how they make them. Individual decisions to be tested or not should not be understood as the output of a rational analysis of the advantages and disadvantages. The decision-making is often gradual, and people could fluctuate between moments of opposition or ambivalence about the test, to others where the consequences are weighed up, for themselves and for others. A provisional position could gradually give way to a feeling of being ready to proceed with the test. In this context, it is therefore possible that the respondents who indicated that they had not yet made a decision were simply at the beginning of such a process. The decision not to undergo genetic testing does not seem to be akin to denial or to disease-avoidance behaviour as suggested by some authors in other comparable contexts [13]. In line with the report of Geelen et al. [17], the results of our survey do not support this hypothesis for different reasons. First, we found that, in the at-risk group, people who consulted a specialist had exactly the same position regarding the diagnosis than people who didn't. Second, a large proportion of individuals at risk were searching for information about CADASIL. Third, over 90% of them were

in close contact with someone with a confirmed diagnosis of the disease. However, we should also notice that a bias possibly related to the non-selection of individuals at risk in the real denial of the disease could not be excluded. In contrast, the concern about the disease taking over their life is by far the most significant factor holding back people at risk from being tested. Two third of individuals at risk claimed their fear that the disease might become too invasive. The burden of self-observation in the lives of those diagnosed with Huntington's disease, even if they state that the onset of Huntington's disease does not seem to be triggered by a newfound awareness of their carrier status, has been already documented [15].

Our survey also asked at-risk subjects about the reasons why they might change their decision not to have a diagnostic test, and on which occasion they might decide to have a genetic test. Apart from the onset of possible symptoms of the disease, as already mentioned, around one third of individuals at risk reported that they might make such a decision if they had to decide to become parents. A similar proportion would choose to be tested if they had a close relative who developed the disease. These results are in accordance with the small number of motivations found to obtain a genetic test in other conditions [24]. The importance of a parental project has been already emphasized in similar contexts [8, 18, 28, 29, 33]. In addition, the clinical manifestations observed in a close relative might contribute to making the disease an inescapable reality. Some studies put forward the desire to reduce uncertainty and anxiety and being in a better position to make decisions and plan for life as shown in the general context of genetic diagnosis of presymptomatic and symptomatic cases [22, 29, 31, 32, 36]. No investigation was previously focused only on individuals at risk who did not undergo diagnostic testing as in our study. Interestingly, the poor impact of pressure from loved ones on the decision to undergo genetic testing was similar to that reported for persons at risk of Huntington's disease [15].

In our survey, most individuals, whether they were at risk or a mutation carrier, expressed their willingness to participate in a clinical trial. Nevertheless, 31% of mutation carriers and 27% of at-risk individuals conditioned their participation on potential side effects and duration of treatment being tested. Interestingly, in one part of our questionnaire, only 37% of individuals at risk responded that the prospect of a clinical trial would lead them to undergo genetic testing while, in another part, 73% would be willing to undergo genetic testing to participate in a clinical trial for testing a drug that could prevent disease progression. How can we explain this discrepancy? The "prospect" of a clinical trial in the first question could have referred to a less tangible situation than an actual participation in a clinical trial, as presented in the second question. This might therefore have justified a more wait-and-see stance. On the other hand, the fact that the second question offered a range of answers allowing respondents to qualify the statement and specify the clinical trials (with or without side effects, longer or shorter) may also have put them in a more realistic situation.

Overall, however, the results suggest that people at risk as mutation gene carriers are a priori relatively open to the possibility of participating in clinical trials. The question of the legitimacy of screening for a serious disease for which there is no treatment has become a hot topic of debate. In the field of Alzheimer's disease, some authors already stressed the potential benefits of genetic screening, particularly in terms of biomarker research, improved prevention or identification of risk factors that could be reduced [1, 2]. Despite the uncertainties regarding biomarkers at preclinical stages of the disease and the potential difficulties in designing secondary prevention trials, the issue is globally approached very optimistically by reducing the ethical questions in relation to presymptomatic diagnosis at individual level to the potential collective benefits of clinical trials. However, this could also be interpreted as a highly questionable transposition of collective benefits to an individual level [10]. The legitimacy of revealing a person's presymptomatic status, when knowledge of the long-term implications remains uncertain, is debatable. Actually, the trade-off between the individual risks (associated with this disclosure in view to participating in clinical trials) and the collective benefits expected from trials in fact, has finally become today a new ethical dilemma [16, 21]. These questions often focus more on the attitude that researchers and doctors should have, than, on the actual point of view of those primarily concerned, i.e., patients. In the context of CADASIL, our results suggest that there is a large variability in the different attitudes to this question, that many people at risk remain clearly uncertain, and that it was is to respect these different points of view and the time needed to make any decision. Other studies, in different socio-economic and cultural contexts, will clearly be needed to develop future trials at presymptomatic stage of CADASIL.

We are aware of different limitations in this study. First, as in virtually all surveys of this type, patients with a special interest in their health status were more prone to participate and women were over-represented (69% among carriers, 77.5% among those at risk) which could partly skew the interpretation of our results. Second, we cannot exclude the influence of the diagnostic protocol in place on certain responses to the questionnaires as already suggested [29]. Within the referral centre, which serves as a model for the management of the disease in France, the respect for 'not knowing' as much as for "wanting to know" is strongly asserted in individuals at risk. Furthermore, the systematic diagnostic procedure for subjects at risk is a long process and requires a real investment on the part of the requesters.

This could reduce the number of requests and lead to more cautious decisions than in a less regulated environment. Finally, these results may apply only to countries with access to sophisticated diagnostic tools and extensive medical insurance cover. We think also that this study has multiple strengths. The survey was not set up by a medical team but was primarily prepared by a team of sociologists who was independent of the diagnostic and management process. They validated with both medical and social workers and the families concerned the different questionnaires they initially designed. This survey made it possible to obtain information from subjects who never consulted and who were not involved in research activities. Moreover, at-risk population comprised both individuals who already had consulted for CADASIL and those who had not. Such a latter subpopulation is distinct from previous approaches adopted in studies analyzing the presymptomatic diagnosis process in similar conditions. Then, our method allowed access to a wide range of people with diverse CADASIL-related experiences.

In summary, the results of this large and independent survey showed that individuals at risk among families do not actually differ from already diagnosed subjects except their younger age and frequent childlessness. They are well informed and in close contact with CADASIL patients and do not seem to be in denial about their personal risk regarding this condition. Most often, they do not undergo genetic testing for fear of being overwhelmed by concerns related to the disease and prefer to delay such a decision to the onset of the first symptoms. Finally, it is as if people at risk put off the shift from indeterminate to patient-in-waiting [34] until the disease makes its presence felt, even if discreetly. From that tipping point onwards, other uncertainties—about how the disease develops or what it is like to be an ill person—take the place of uncertainty about status [16, 21]. Reasons that could lead to a diagnostic decision other than the appearance of symptoms could then vary widely and might depend for example on the decision to become parents or on the experience of the disease in a close symptomatic relative. Finally, although the interest of subjects at risk in therapeutic development is as high as in CADASIL patients and indisputable, the influence of a possible participation in a therapeutic trial on such a decision appears ambiguous and uncertain. At first sight, such results might seem to compromise the recruitment of asymptomatic people in future clinical trials, as it would require them to engage in early diagnosis. It cannot be ruled out, however, that a more favorable scenario leading to acceptance of a proposal could take place after further reflection and in a real and very concrete situation.

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Data availability Not applicable.

Declarations

Conflicts of interest The authors declared that they have no conflict of interest related to this work.

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