



# Psychological impact of COVID-19 containment on CADASIL patients

S. Reyes<sup>1</sup> · A. Jabouley<sup>1</sup> · N. Alili<sup>1</sup> · M. H. De Sanctis<sup>1</sup> · C. Machado<sup>1</sup> · A. Taleb<sup>1</sup> · D. Herve<sup>1</sup> ·  
N. Dias-Gastellier<sup>1</sup> · H. Chabriat<sup>1,2</sup>

Received: 16 January 2023 / Revised: 22 February 2023 / Accepted: 23 February 2023 / Published online: 4 March 2023  
© The Author(s) 2023

## Abstract

**Introduction** COVID-19 restrictive containment was responsible for major psychological distress and alteration of quality of life (QoL) in the general population. Their impact in a group of patients having cerebral small vessel disease (SVD) and at high risk of stroke and disability was unknown.

**Objective** We aimed to determine the potential psychological impact of strict containment during the COVID-19 pandemic in a sample of CADASIL patients, a rare SVD caused by NOTCH3 gene mutations.

**Methods** Interviews of 135 CADASIL patients were obtained just after the end of the strict containment in France. Depression, QoL and negative subjective experience of the containment were analysed, as well as predictors of posttraumatic and stressor-related manifestations, defined as an Impact Event Scale-Revised score  $\geq 24$ , using multivariable logistic analysis.

**Results** Only 9% of patients showed a depressive episode. A similar proportion had significant posttraumatic and stressor-related disorder manifestations independently associated only with socio-environment factors, rather than clinical ones: living alone outside a couple (OR 7.86 (1.87–38.32)), unemployment (OR 4.73 (1.17–18.70)) and the presence of 2 or more children at home (OR 6.34 (1.35–38.34)).

**Conclusion** Psychological impact of the containment was limited in CADASIL patients and did not appear related to the disease status. About 9% of patients presented with significant posttraumatic and stressor-related disorder manifestations which were predicted by living alone, unemployment, or exhaustion related to parental burden.

**Keywords** COVID-19 · Cerebral small vessel disease · CADASIL · Stroke · Depression · PTSD

## Introduction

In France, at the heart of the COVID-19 epidemic in 2020 and well before the emergence of vaccination, major psychological distress and significant impairment of quality of life occurred in the general population at time of the containment [18, 27]. The most restrictive measures of containment occurred that year from March 17 and lasted 8 weeks. Accumulating data showed that populations under this lockdown could develop various mental disturbances, sleep difficulties,

anxiety and posttraumatic and stressor-related disorder manifestations [41, 42, 44, 47]. Decompensation of premorbid psychiatric conditions and addictive behaviours were also frequent [6, 27]. In the Chinese population, 76% of individuals felt moderate-to-severe negative consequences using a self-report measure of posttraumatic subjective distress [41]. The analysis of such consequences was further complicated by the fact that the viral infection itself could also affect the brain tissue and lead to neuropsychiatric manifestations at individual level [19, 28, 34].

Predicting the negative impact of containment on the quality of life and psychological health was then crucial for developing preventive strategies at individual or familial level or specific policies at population level [6, 33, 42, 47]. Multiple predictors have been already identified in the general population, they were relating to age, sex, pre-existing psychological status, changes in the circadian rhythms, familial and social support, professional status, education level as well as cultural aspects [5, 20, 35, 36, 42]. Other

✉ H. Chabriat  
hugues.chabriat@aphp.fr

<sup>1</sup> CNVT and Department of Neurology and Referral Center for Rare Vascular Diseases of the Brain and Retina (CERVCO), Hôpital Universitaire Lariboisière, Assistance Publique des Hôpitaux de Paris, GHU-Paris-Nord, APHP, 2 Rue Ambroise Paré, 75010 Paris, France

<sup>2</sup> INSERM U1141–FHU-NeuroVasc, Paris, France

factors are related to the living conditions such as the ability of teleworking, potential of home schooling, variety of occupational activities or exposure to daily information [14, 25, 28, 30, 33, 45].

At the end of the strict containment in France, we chose to investigate patients with a genetically-confirmed diagnosis of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). CADASIL is caused by mutations of the NOTCH3 gene that stereotypically lead to vascular accumulation of the derived protein products around smooth muscle cells and pericytes in the wall of cerebral microvessels [21, 22]. The disease is responsible for attacks migraine with aura, transient ischaemic attacks, repeated stroke and various psychological disturbances starting in midadulthood (mostly mood changes, anxiety and apathy). It leads progressively, after 50 to 60 years, to severe motor and cognitive decline [11].

At the beginning of the COVID-19 pandemic, CADASIL patients were informed that they were particularly exposed to an increased risk of stroke [40, 43, 46] since the viral infection could promote severe vascular inflammation and thrombosis [13]. We then hypothesized that CADASIL patients, who are already prone to anxiety and mood disturbances [8], might be particularly distressed during the very strict quarantine imposed at the onset of the COVID pandemic. Thus, we undertook a detailed survey for evaluating the psychological status and quality of life of these patients just at the end of the strict containment, together with their clinical status, social situation and daily living conditions during this time-frame.

The present study aimed at estimating the importance of distress in CADASIL patients during this exceptional event and to delineate potential predictors.

## Methods

### Subjects

Patients were selected based on the following inclusion criteria: (1) age higher than 18 years, (2) diagnosis confirmed by a genetic test and showing a typical cysteine mutation of the NOTCH3 gene, (3) participation to the French Cohort of CADASIL patients evaluated in the National Referral Centre for rare cerebrovascular diseases ([www.cervco.fr](http://www.cervco.fr)); (4) having at least two previous follow-up visits in the centre, (5) lack of sensory or severe cognitive difficulties (particularly in reasoning, language or attention) that could compromise the understanding of questions, (6) French language skills allowing easy understanding of questions asked by phone, (7) informed consent already obtained for collecting clinical and imaging data during follow-up. Patients already known having dementia (defined by DSM-IV-TR criteria [3]),

severe motor disability and who were highly dependent in daily life were excluded from the outset.

### Evaluation procedure

An experienced physician (NA) assessed all potential candidates who were pre-selected from the cohort on a first telephone interview. On this occasion, clinical information were updated for each subject, particularly any recent history of migraine with aura, stroke, mood disturbances and cognitive difficulties as well as the severity of disability based on the modified Rankin Scale (mRS) using a structured questionnaire [15]. Ongoing treatments including psychotropic medication were finally noticed. Thereafter, the physician checked whether the patient was willing and consent to be contacted by telephone and interviewed by a psychologist of the CERVCO team. The evaluation was then performed by experienced psychologists (SR, AJ, MH, CM) based on individual telephone interviews of 1–2 h, no later than 6 weeks after the end of the strict containment that occurred in France between 17th march and 10th may 2020.

### Information collected

A specific questionnaire dedicated to the pandemic situation was specifically developed based on the literature available at that time and considering the specificities of the genetic disease. The different questions and items were established by consensus among all the authors of the present report who had a long-term experience in the care of CADASIL patients (Table 1). This questionnaire provided 3 different scores reflecting key issues regarding the containment: score 1—the level of stressors the patient was confronted with, score 2—the level of risk related to viral contamination and clinical worsening during the containment, score 3—the level of her/his subjective experience of the containment considered as negative. The score related to the level of stressors was varying between 0 (low) and 10 (high). Both the material conditions, isolation and stressing events were assessed, particularly, isolation or overcrowding in the patient's residence, teleworking at home with or without the need of organising children's schooling, possibility of outdoor access (terrace or garden), difficulties in the economic situation including loss of employment, lack of contact with loved ones, occurrence of a severe form of COVID19 infection or death in close relatives of friends, difficulties in accessing health services. The second score related to the risk of worsening of health status associated to potential viral infection was varying from 0 (low) to 3 (high). This score was based on the evaluation of the COVID19 virus circulation around the patients and occurrence of infection in the patient. Finally, the third score related to the level of negative experience of containment could vary from 0

**Table 1** Questionnaire developed by the CERVCO team and used by the psychologists for interviewing the CADASIL patients

Scoring	0	1
<b>Level of stressors previously identified in the general population related to the negative impact of containment</b>		
Were you living alone during the containment?	No	Yes
How many persons per room were you during the containment?	<3	≥3
Did you have access to an open space (garden or balcony) during the containment?	Yes	No
Did you do teleworking during the containment?	No	Yes
Did you do teleworking while taking care of your children's schooling during the containment?	No	Yes
Did you loose your job due to the COVID-19 outbreak?	No	Yes
Did your socio-economic situation get worse because of the lockdown?	No	Yes
Did you hear from your loved ones during the containment?	Yes	No
Have any of your loved ones died or been in intensive care due to COVID-19?	No	Yes
Since the start of the epidemic, did you have difficulties to access medical care?	No	Yes
<b>Level of contamination in the patient's environment during the containment</b>		
Did you have numerous COVID-19 cases in your regional area during the containment?	No	Yes
Has anyone close to you been tested positive for COVID-19 during the containment?	No	Yes
Were you personally tested positive for COVID-19 during the containment?	No	Yes
<b>Level of negative subjective experience during the containment</b>		
Did you feel or perceive any positive aspect (s) during the containment ?	Yes	No
During the containment, did you consider your isolation as particularly difficult ?	No	Yes
Do you think that your cerebrovascular illness made this containment's experience worse ?	No	yes
Do you think that media information was particularly anxiety-inducing during the containment?	No	yes
Did the containment completely disrupt your daily routines?	No	yes
During confinement, did you feel that your motivations were still intact?	Yes	No
During the containment, did you feel that your life will never be the same again?	No	yes

to 7, 7 corresponding to the worst experience of isolation the patient has ever had. This score was estimated based on the global feeling of isolation, perception that the cerebrovascular disease worsened this isolation, perceived anxiety related to daily news received from the media, difficulties in establishing daily routines, lack of motivation in everyday life and feeling that life will never be the same as before.

In addition to the questionnaire, quality of life was evaluated using the Euro-QoL [32], a standardised self-rated measure of quality of life related to the health status. We used the global measure of health status which was rated on a vertical visual analogue scale from 0, corresponding to the “worst imaginable health state”, to 100% corresponding to the ‘best imaginable health state’. We also used the anxiety/depression dimension having 3 levels of perceived difficulties (1: no problem, 2: some problems and 3: extreme problems). The French version of the Montgomery and Asberg Depression Rating Scale (MADRS) was used as a hetero scale assessing intensity of depressive symptoms from 0 (low) to 60 (severe) [12, 29]. The presence of a major depressive disorder was confirmed based on both a structured psychological interview assessing the corresponding DSM V depression criteria [1] and a MADRS score higher than 8, corresponding to mild

symptoms [24, 38]. To assess traumatic and stressor-related symptomatology, psychologists applied by telephone the French version of the Weiss Impact of Event Scale (IES-Revised) [7, 42], a 22-item self-report measure widely used to assess multiple symptoms and particularly subjective distress caused by traumatic or stressor events. The IES-R yields a total score (ranging from 0 to 88) including 3 subscale scores for intrusion, avoidance, and hyperarousal, the core symptoms of posttraumatic stress disorder (PTSD). In the present study, a cut-off score equal or higher than 24 was considered as significant posttraumatic or stressor manifestations and a score higher than 33 as compatible with the diagnosis of PTSD [9].

Data obtained before the containment regarding the psychological status of all voluntary patients were also extracted from the database, the educational level and particularly the history of depressive episodes, degree of anxiety, global cognitive status, and quality of life at the last clinical follow-up preceding the containment. Additional data that may influence the effects of containment at individual level such as the marital status (living in couple or not), general socio-demographic characteristics (active life, retirement or unemployment) and number of children at home during the containment were also recorded.

## Statistical analysis

Data were first described using their percentage, mean, standard deviation, median, first and third quartile values. Normality was assessed with graphic analysis and the normal quantile plot and tested using the Shapiro Wilk test when needed.

Univariate analysis was then performed for comparison of socio-demographic and clinical data before containment and of severity of disability, depression and quality of life at time of the survey, between patients with IES-R score higher or equal to 24 and the others. The comparison was performed based on the Exact Fisher's test for categorical variables, the Student's *t* test for continuous variables of normal distribution and the Wilcoxon test in the absence of normality. Paired samples Wilcoxon test (signed rank test) was used to assess whether a significant modification of the modified Rankin Scale, the Anxiety/Depression levels of EQ5, the occurrence of a major depression or the quality of life changed between the last follow-up visit and the results obtained at time of containment.

Multivariable binomial logistic models were fit to find the final and best model using the Akaike criterion to predict the presence of significant posttraumatic stress manifestations (IES-R  $\geq 24$ ) after selection of factors among those with *p* value  $< 0.25$  in the previous univariate analysis. Only variables with less than 5% of missing values were used in the analysis. The missing data, if any, were replaced using five replicate imputations based on the chained equation method for multiple imputation (package mice with R). The model was internally validated using bootstrapping. Statistical analysis was performed using JMP14.3 (SAS) and RStudio, 2022.12.0.

## Results

### Patients' clinical status before containment

Among 358 patients included in the cohort, 202 patients were eligible based on our selection criteria. Among these individuals 6 were already deceased at time of the study, 5 had become demented, 45 cases could not be contacted by telephone and 11 refused to participate. One hundred and thirty-five patients of mean age  $57 \pm 12$  years (SD) were included in this study. None of them had been infected with covid19 before the interview. The main characteristics of the population are detailed in Table 2. The median time interval between the last follow-up visit at the referral centre and the neuropsychological evaluation was 21 months. Two third of patients were women, the same proportion was living in couple, 40% had a high level of education, one third were already retired while 14% were unemployed, all

had children. At clinical level, the mean MMSE score was  $28 \pm 2.5$  but ranged from 11 to 30. Globally, patients were not severely disabled, the mRS score was 0 to 1 in 3 out of 4 patients, only 9 patients had a moderate or severe disability. Fifty one percent of patients did not previously suffer from a stroke event and one in five patients currently used an anxiolytic or an antidepressant drug. About 16% of selected individuals already experienced a major depressive episode.

### Negative subjective experience during the containment in the whole sample

Based on our dedicated questionnaire, only 15 patients had a level higher than 5 of negative subjective experience during the containment (score 3). A fraction of 15 to 20% of the sample had a level of 1, a similar fraction had a level 2, 3 and 4. Less than 5% did not experience any negative feeling. The level of this negative subjective experience was not related to the number of stressors presumably related to the negative impact of containment in the general population [(spearman rank ( $\rho = -0.0454$ ,  $p = 0.6013$ )] nor to the level of contamination in the patient's environment [( $\rho = -0.0998$ ,  $p = 0.247$ )] (Fig. 1).

### Psychological manifestations just after the containment in the whole sample

At the time of the survey, only 9% of patients ( $n = 12$ ) were suffering from a major depressive episode. Two among the latter, who did not previously experience depression, were using an antidepressant treatment. Only three already experienced depression but were not treated. Of the 21 patients who were depressed at the last visit before the interview, only 6 continued to use an antidepressant, 18 were no longer affected during the containment period.

In the whole population, 21% of patients ( $n = 28$ ) were currently using psychoactive drugs. When they were treated by an antidepressant drug, more than 90% of patients were using a selective serotonin reuptake inhibitor (SSRIs) (paroxetine, escitalopram, fluoxetine or sertraline). Only 3% of individuals were daily using anxiolytics (benzodiazepine drugs) and only one patient was treated by an antipsychotic drug (Table 1).

Although depression was less present in the whole sample after the containment than before (difference of means ( $\delta = 0.08$ ,  $p = 0.02$ ), a small but significant increase of the mRS score ( $\delta: 0.20$ ,  $p < 0.02$ ) and of the MADRS score ( $\delta = 2.6$ ,  $p = 0.0033$ ) was detected at time of the survey. Conversely, the variation between pre and post-containment of the Euroquol global visual score and of the Euroquol quantitative score evaluation of anxiety/depression dimension did not vary significantly in the whole sample ( $\delta = 0.02$ ,  $p = 0.9$  and  $\delta = 0.07$ ,  $p = 0.22$  respectively).

**Table 2** Sociodemographic and clinical features of the study individuals at the time of the survey

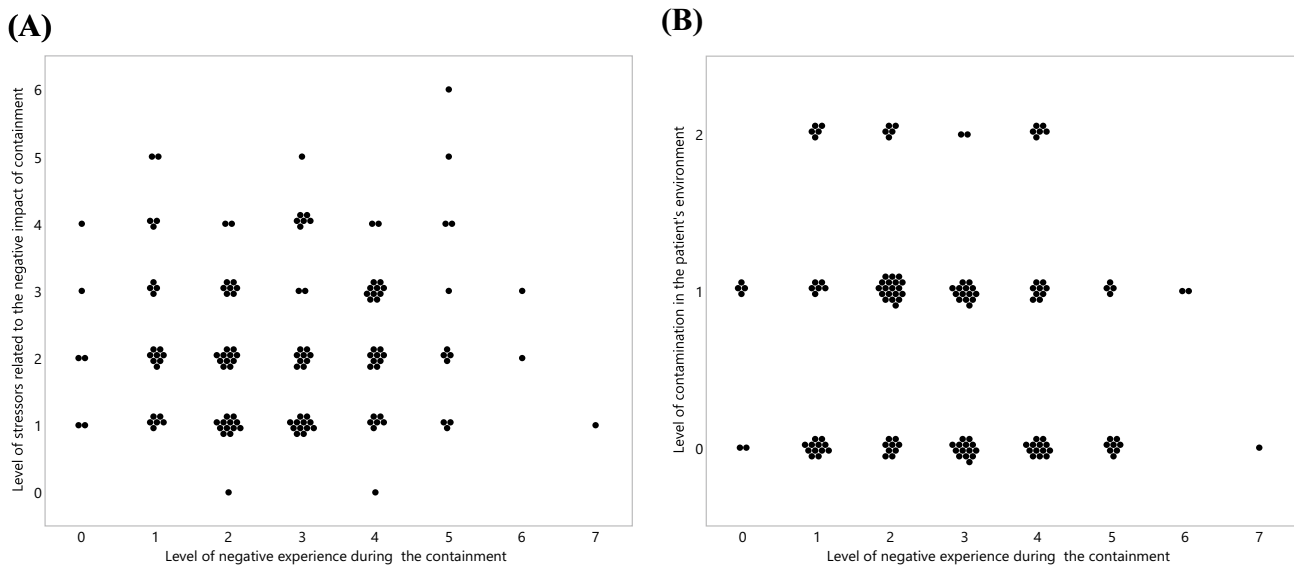
Age mean (SD), median(Q <sub>25</sub> –Q <sub>75</sub> )	57.9 (11.9), 58 (48–69)
Gender: women	65.1% ( <i>n</i> = 88)
Education level (number of years at school)	
Range (median, Q <sub>25</sub> –Q <sub>75</sub> ); Mean (Sd)	12.2 (3.6), 4–22 (12–15)
High level of education (≥ 12 years)	40.2% ( <i>n</i> = 54)
<b>Marital status during confinement</b>	
Not in couple-alone	34.8% ( <i>n</i> = 47)
Living in couple	65.1% ( <i>n</i> = 88)
<b>Socioprofessional category</b>	
Active working	50.3% ( <i>n</i> = 68)
Unemployment	14.1% ( <i>n</i> = 19)
Retirement	35.5% ( <i>n</i> = 48)
<b>Number of children</b>	
None	0%
One	46.6% ( <i>n</i> = 63)
Two or more	53.3% ( <i>n</i> = 72)
<b>Previous stroke events</b>	
None	51.1% ( <i>n</i> = 69)
One	32.5% ( <i>n</i> = 44)
Two or more	16.3% ( <i>n</i> = 22)
History of migraine (all types)	42.9% ( <i>n</i> = 58)
<b>Modified Rankin Scale</b> ( <i>n</i> = 119)	
0–1	74.8% ( <i>n</i> = 89)
2	17.8% ( <i>n</i> = 21)
3–4	7.5% ( <i>n</i> = 9)
Anxiety/depression perception (Euro-Quol Dimension 5), levels 1, 2, 3	50%, 43%, 7%
Major depressive disorder	9% ( <i>n</i> = 28)
MADRS Score, Mean (Sd), MEDIANE (Q <sub>25</sub> –Q <sub>75</sub> )	11.0 (9.9), 8 (2–18)
Current use of psychoactive drugs, % ( <i>N</i> )	21.4% ( <i>n</i> = 29)
Antidepressant % ( <i>N</i> )	17.7% ( <i>n</i> = 24)
Anxiolytic, % ( <i>N</i> )	2.9% ( <i>n</i> = 4)
Antipsychotics, % ( <i>N</i> )	0.7% ( <i>n</i> = 1)
Quality of life( EuroQuol Analogue Visual Scale) MEAN (SD), MEDIANE (Q <sub>25</sub> –Q <sub>75</sub> )	70.5 (18.8), 70 (60–85)

### Frequency and predictors of posttraumatic or stressor-related manifestations (partial posttraumatic disorder and probable posttraumatic disorder)

One patient did not provide all answers to the IES-R questionnaire, in the other 134 patients, the mean IES-R was  $9.4 \pm 10.7$  (median: 5, Q1–Q4: 2–14). Only 13 patients, had an IES-R score larger than or equal to 24. Among them, 7 had a score equal or higher than 33. These two groups were compared to patients with IES-R less than 24 (Table 3). Patients with IES-R score  $\geq 24$  had a higher Anxiety/Depression EQ5 level, were 5 times more often depressed and had a higher MADRS score than patients with IES-R score less than 24. In contrast, the mRS and Visual Euroqol scores did not differ between these groups. The different IES-R subscores were all increased without

any distinction for one of the 3 subscores. Similar contrasts were observed when the analysis was restricted to patients with IES-R score  $\geq 33$ .

Multivariable analysis showed that the best predicting model of IES-R  $\geq 24$  in patients (ROC curve AUC = 0.81) included 4 factors, 3 of which were predictors of significant post-stress manifestations: (1) the status of unemployment (OR = 4.73,  $p < 0.03$ ), (2) the status of being single and not in couple (OR = 7.86,  $p = 0.0047$ ) and (3) the fact to have more than one child (OR = 6.34,  $p = 0.018$ ) at home during the containment (Table 4). The different clinical parameters that differ in univariate analysis according to the level of IES-R did not improve the prediction model. No interaction was detected between the factors identified. Internal model validation showed a Somers D value of 0.643, c index of 0.822 (proportion of patients ordered correctly by the model) and  $R^2$  of 0.373.



**Fig. 1** Distribution of cases showing the level of negative experience during the containment according to the level of stressors (A) or to the level of viral contamination (B)

## Discussion

The results of this study showed that the strict containment ordained in France over 8 weeks in 2020 to reduce the COVID 19 contamination had, globally, a limited impact on mental health in a sample of CADASIL patients. Just at end of the containment, only 9% of individuals were found depressed whereas this frequency was about 16% at their last follow-up visit. More specifically, 18 patients who were previously depressed were no longer affected at time of the containment. This low prevalence contrasts with the 16.5% frequency of depression estimated in a survey obtained in the general population at the initial outbreak among 1738 respondents from 190 Chinese cities [42]. It was also lower than the 17% prevalence of depression estimated in the general population using an internet-based-questionnaire in Italy just after the first lockdown measures [35]. Differences in the definition of depression, type of survey and selection biases among responders might well explain this discrepancy. It should also be noted that 21% of the cohort individuals were already treated by an antidepressant or an anxiolytic drug at time of containment which could have significantly mitigated the impact of the lockdown on mood of CADASIL patients. In line, only a small increase of the MADRS score was detected in the whole cohort at end of the containment, without any significant impact on the quality of life. The degree of negative experience felt related to this exceptional event was assessed at individual level. A score higher than 5 was obtained only in 15 patients based on 7 specific questions related to the lack of positive output, degree of isolation, risk for health, anxiogenic daily news,

routine disruption, demotivation and global life-altering effect in relation to the containment [17, 33, 41, 47]. This discomfort did not appear related to the number of stressors nor to the risk level of viral contamination in the CADASIL patient's environment. Altogether, these data support that the immediate effects of containment were actually limited in this sample of patients, that there was no effect on the frequency of major depressive episodes, and some psychological impact limited to a subgroup of individuals.

Exposure to an exceptional event as the “lockdown” could also have precipitated transient or more enduring psychological manifestations related to posttraumatic stress or stressor-related disorder independently from depression [16]. The mean IES-R score of 9.4 measured in our CADASIL patients was 3 times lower than that reported in a much larger number of volunteers at time of the outbreak in China [42]. Our result was much closer to the mean IES-R value measured among non-medical health care workers during the COVID crisis in Singapore and which was twice higher than that detected in the medical staff in the midst of the COVID 19 outbreak [39]. In the present study, 13 out of 135 CADASIL patients had an IES-R score equal or higher than 24, a level considered as best predicting the occurrence of significant manifestations of a posttraumatic stress disorder [4]. Among them, 7 reached a score higher than 33, a cut-off that provides a good accuracy level for PTSD [9]. They also showed, as expected, that CADASIL individuals with significant posttraumatic or stressor-related manifestations had a higher MADRS score and were 5 times more depressed than the other patients.[9]. In this subgroup of patients,

**Table 3** Impact of Event Scale Revised: contrasting features between patients with score < 24, ≥ 24 and ≥ 33

IES-R global score limits	< 24 (n = 121)	≥ 24 (n = 13)	P value	≥ 33 (n = 7)	p value <sup>a</sup>
<b>Sociodemographic aspects</b>					
Age	58.04 ± 11.95	55.23 ± 11.07	0.389	53.8 ± 10.83	0.33
Female sex	<b>62%</b>	<b>100%</b>	<b>0.003</b>	<b>100%</b>	<b>0.04</b>
Education years > 12	41%	31%	0.563	43%	1
Living alone vs in couple	<b>32%</b>	<b>62%</b>	<b>0.036</b>	<b>71%</b>	<b>0.04</b>
<b>Professional status</b>					
Active working	<b>53%</b>	<b>31%</b>	<b>0.012</b>	<b>43%</b>	<b>0.09</b>
Unemployment	<b>11%</b>	<b>43%</b>		<b>43%</b>	
Retirement	<b>36%</b>	<b>26%</b>		<b>14%</b>	
Two children or more	52%	77%	0.088	57%	1
<b>Clinical data available before containment</b>					
MMSE score	28.1 ± 2.6	27.5 ± 2.3	0.31	28.3 ± 1.97	0.81
Previous stroke events	49%	46%	1	42%	0.74
Past history of migraine	43%	39%	0.776	14%	0.24
mRS (2–5 vs 0–1)	<b>21%</b>	<b>53%</b>	<b>0.021</b>	40%	0.32
Anxiety/Depression (EQ 5) Levels 1, 2, 3	46–46–8%	23–61–15%	0.252	43–43–28%	0.19
Major depressive disorder	16%	23%	0.450	14%	1
MADRS score	<b>7.76 ± 7.23</b>	<b>12.5 ± 2.12</b>	<b>0.07</b>	11.72	0.26
Quality of life(EuroQuol Analogue Visual Scale)	71 ± 18	62.7 ± 22.9	0.21	69 ± 27	0.84
<b>Information at time of containment</b>					
mRS (2–5 vs 0–1)	34%	46%	0.54	28%	0.8
Anxiety/Depression (EQ Dimension 5) Levels 1, 2, 3	<b>54–43–3%</b>	<b>15–46–38%</b>	<b>0.0003</b>	<b>14–14–43%</b>	<b>&lt; 0.0001</b>
Major depressive disorder	<b>6%</b>	<b>31%</b>	<b>0.01</b>	<b>43%</b>	<b>0.01</b>
MADRS	<b>9.98 ± 9.69</b>	<b>20.40 ± 7.79</b>	<b>0.003</b>	<b>21.9 ± 7.9</b>	<b>0.003</b>
Quality of life( EuroQuol Analogue Visual Scale)	70.42 ± 19.28	62.0 ± 5.58	0.29	60.28 ± 29.42	0.41
Level of stressors > 4	15%	23%	0.42	14%	1
Level of contamination	56%	61%	0.77	71%	0.69
Level of negative experience > 5	9%	23%	0.17	14%	0.53
IES-R subscore intrusion	<b>2.6 ± 2.8</b>	<b>12.9 ± 4.4</b>	<b>&lt; 0.0001</b>	<b>14.1 ± 5.3</b>	<b>&lt; 0.0001</b>
IES-R subscore avoidance	<b>2.0 ± 2.8</b>	<b>11.2 ± 6.3</b>	<b>&lt; 0.0001</b>	<b>13.6 ± 6.9</b>	<b>&lt; 0.0001</b>
IES-R subscore hyperarousal	<b>2.1 ± 2.6</b>	<b>10.6 ± 5.4</b>	<b>&lt; 0.0001</b>	<b>13.5 ± 4.7</b>	<b>&lt; 0.0001</b>

Significant differences are in bold

<sup>a</sup>Comparison with the reference group IES-R, Wilcoxon Rank tests were used for continuous values, Fischer's Exact test for %

**Table 4** Results of multivariate regression analysis (3 significant predictors–AUC=0.821)

Term	Estimate	SE	Chi2	p Chi2	Lower 95%	Upper 95%	Odds Ratio	p	Lower 95%	Upper 95%
Intercept	– 3.69	0.95	15.01	0.0001*	– 5.84	– 2.05	–	–	–	–
Unemployment vs work/retirement	– 0.78	0.35	5.01	0.0252*	– 1.46	– <b>0.08</b>	<b>4.73</b>	<b>0.0295*</b>	<b>1.17</b>	<b>18.70</b>
Alone vs Couple	1.03	0.38	7.39	0.0066*	0.31	<b>1.82</b>	<b>7.86</b>	<b>0.0047*</b>	<b>1.87</b>	<b>38.32</b>
More than 1 child	1.85	0.83	4.90	0.0269*	0.30	<b>3.65</b>	<b>6.34</b>	<b>0.0180*</b>	<b>1.35</b>	<b>38.34</b>
Anxiety/Depression (EQ 5) Levels 1 vs 2/ 3	1.09	0.76	2.05	0.15	– 0.31	2.75	2.95	NS	0.73	15.71

Significant differences are in bold

the reduction of quality of life was limited and did not reach statistical significance as also the increase level of negative experience. The parallel increase of the 3 IES-R subscores suggest that the development of posttraumatic or stress manifestations does not follow a specific pattern but involved both hyperarousal physical symptoms, avoidance behaviours to contain the distress and intrusive distressing memories, in a similar way.

CADASIL patients with posttraumatic or stressor-related manifestations were found more frequently to be women, living alone, unemployed, and having more neurological disability in univariate analysis. However, only 3 socio-environmental factors predicted independently the occurrence of posttraumatic or stressor-related manifestations. All these factors had been already recognized as potentially capable to precipitate the occurrence of stress manifestations during the COVID 19 pandemic in the general population [17, 33, 41, 47]. First, CADASIL patients who were living alone were found to present posttraumatic or stressor-related symptoms nearly eight times more frequently than patients who were living in a couple. Outside this context of COVID pandemic, singlehood has been already shown to have a considerable impact on the psychological health of individuals in the general population [2]. In individuals living alone, the lockdown situation obviously aggravated this isolation by reducing or completely eliminating the interactions which were previously maintained through working activities [31, 37]. The absence of a close partner with whom the patient can share his/her impressions, routines of daily life, hobbies and can discuss the information received through the media appears to be particularly deleterious. Second, the results showed that CADASIL patients who were unemployed were 4.7 times more likely to develop posttraumatic or stressor-related symptoms than the rest of the sample. Clearly, unemployment had probably further aggravated the social isolation during the lockdown and was already shown to be a major concern during the COVID pandemic in a previous UK-based focus group study [44]. The unemployed situation increases the uncertainty felt by the patient about his/her social reintegration and his/her future. It can also aggravate or decompensate an already precarious economic situation, another source of psychological stress [26]. Third, patients who had two children and more at home were about 6 times more likely to develop posttraumatic or stressor-related manifestations than the rest of the population. This could be related to the difficult management of organising courses and working at home in parallel, to the inherent communication problems depending on the quality of the technical installation, access to internet, and schedules, but also to the difficulty in maintaining the attention of children for hours of work for lessons at home in these circumstances [10, 23]. The premises, the number of people per room, the

noise generated by the various activities, are all potential additional sources of complications.

We are fully aware of different weaknesses of the present study. The selection of our patients was necessarily biased because we chose to investigate only individuals from a cohort of volunteers, who already accepted to be followed and for whom information could be easily collected. Thus, this sample could not represent the whole population of CADASIL patients. Moreover, the study population was relatively small in size which prevented the identification of other predictors of post-containment manifestations. We also did not validate externally the present results in an independent population. Thus, it is most likely that the present findings might not be transposed to a different CADASIL cohort in a distinct social, cultural or political context. For instance, the lack of predictors related to the clinical or psychological status observed in the present study might be specifically related to the situation of individuals who were diagnosed in France, who could benefit from a 100% coverage of all their health care costs as well as a full wage replacement throughout the entire period of containment. The present study also had a number of strengths. All investigations were carried out in a homogeneous population corresponding to patients at the highest risk of decompensation who already had a confirmed genetic diagnosis of their disease and without major disability. This study was also based on clinical tools and scores already validated. Detailed clinical information were available for each individual. Clinical and psychological information were updated and collected through direct intervention of professionals with a long expertise in the management of CADASIL. The results were also coherent. They showed without any ambiguity the importance of socio-environmental factors that could worsen the psychological status of CADASIL patients during the lockdown period.

## Conclusion

In conclusion, we believe that the results of this study support that isolation of CADASIL patients, unemployment and the number of children at home should be considered to evaluate the risk of psychological distress during exceptional situations leading to social breakdown as the containment.

**Author contributions** SR: study design, planning, investigations, data analysis, drafting. sonia.reyes@aphp.fr. AJ: study design, investigations, writing. aude.jabouley@aphp.fr. NA: investigations, drafting. nassira.alili@aphp.fr. M-HDES: investigations, writing. marie-helene.desanctis@aphp.fr. CM: investigations, writing. carla.machado@aphp.fr. DH: investigations, writing. dominique.herve@aphp.fr. AT: data verification. abbas.taleb@aphp.fr. ND-G: study design, project



administration, study organisation, drafting.nathalie.gastellier@aphp.fr. HC: study design, funding, data analysis, supervision, drafting. hugues.chabriat@aphp.fr.

**Funding** This research was supported by the ANR grant: RHU TRT\_cSVD (ANR:16-RHUS-0004) and also by the Association ARNEVA (Association de Recherche en Neurologie Vasculaire).

**Data availability** Data related to this study are available upon request.

## Declarations

**Conflicts of interest** The authors declare that they have no conflict of interest.

**Ethical standard statement** This study has been approved by the Institutional Review Board (IRB000038888) of the French Institute of Medical Research and Health and was performed in accordance the Declaration of Helsinki and the STROBE reporting guidelines.

**Consent to participate** All patients gave their informed consent prior to the inclusion in the study.

**Consent for publication** All authors have approved the manuscript for submission; accordingly, the manuscript conforms to the journal's policies. The authors take full responsibility for the data, the analyses and interpretation, and the conduct of the research. They have full access to all data, and the right to publish any and all data separate and apart from the guidance of any sponsor.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

1. DSM-5 - Manuel diagnostique et statistique des troubles mentaux 5 edition. In: Crocq M-A, Guelfi J-D, Boyer P, Pull C-B, Pull M-C (eds) American Psychiatric Association, Masson, France
2. Adamczyk K (2017) Voluntary and involuntary singlehood and young adults' mental health: an investigation of mediating role of romantic loneliness. *Curr Psychol* 36:888–904
3. Association AP (2000) Diagnostic and statistical manual of mental disorders, 4th edition, text revision (DSM-IV-TR). American Psychiatric Association
4. Asukai N, Kato H, Kawamura N, Kim Y, Yamamoto K, Kishimoto J, Miyake Y, Nishizono-Maher A (2002) Reliability and validity of the Japanese-language version of the impact of event scale-revised (IES-R-J): four studies of different traumatic events. *J Nerv Ment Dis* 190:175–182
5. Bendau A, Kunas SL, Wyka S, Petzold MB, Plag J, Asselmann E, Strohle A (2021) Longitudinal changes of anxiety and depressive symptoms during the COVID-19 pandemic in Germany: the role of pre-existing anxiety, depressive, and other mental disorders. *J Anxiety Disord* 79:102377
6. Blithikioti C, Nuno L, Paniello B, Gual A, Miquel L (2021) Impact of COVID-19 lockdown on individuals under treatment for substance use disorders: Risk factors for adverse mental health outcomes. *J Psychiatr Res* 139:47–53
7. Brunet A, St-Hilaire A, Jehel L, King S (2003) Validation of a French version of the impact of event scale-revised. *Can J Psychiatry* 48:56–61
8. Chabriat H, Lesnik Oberstein S (2022) Cognition, mood and behavior in CADASIL. *Cereb Circul Cognit Behav*
9. Creamer M, Bell R, Failla S (2003) Psychometric properties of the impact of event scale - revised. *Behav Res Ther* 41:1489–1496
10. Delgado-Ortiz L, Carsin AE, Merino J, Cobo I, Koch S, Goldberg X, Chevance G, Bosch de Basea M, Castano-Vinyals G, Espinosa A, Carreras A, Cortes Martinez B, Straif K, de Cid R, Kogevinas M, Garcia-Aymerich J (2022) Changes in population health-related behaviors during a COVID-19 surge: A Natural Experiment. *Ann Behav Med*
11. Dupe C, Guey S, Biard L, Dieng S, Lebenberg J, Grosset L, Alili N, Herve D, Tournier-Lasserre E, Jouvent E, Chevret S, Chabriat H (2022) Phenotypic variability in 446 CADASIL patients: Impact of NOTCH3 gene mutation location in addition to the effects of age, sex and vascular risk factors. *J Cereb Blood Flow Metab*
12. Farner L, Wagle J, Flekkoy K, Wyller TB, Fure B, Stensrod B, Engedal K (2009) Factor analysis of the Montgomery Aasberg Depression Rating Scale in an elderly stroke population. *Int J Geriatr Psychiatry* 24:1209–1216
13. Fotuhi M, Mian A, Meysami S, Raji CA (2020) Neurobiology of COVID-19. *J Alzheimers Dis* 76:3–19
14. George M, Baby N, Azad A, Rajan A, Radhakrishnan SK (2021) Neurological disorders seen during second wave of sars-cov-2 pandemic from two tertiary care centers in Central and Southern Kerala. *Ann Indian Acad Neurol* 24:917–926
15. Godefroy O, Just A, Ghitu A, Leclercq C, Garcia PY, Lamy C, Canaple S, Bugnicourt JM (2012) The Rankin scale with revised structured interview: effect on reliability, grading of disability and detection of dementia. *Int J Stroke* 7:183
16. Green BL, Solomon SD (1995) The mental health impact of natural and technological disasters. In: Freesly JR, Hobfall SE (eds) *Traumatic stress: from theory to practice*. Plenum Press, New York, pp 163–180
17. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS, China Medical Treatment Expert Group for C (2020) Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* . 2020 Apr 30;382(18):1708–1720.
18. Haesebaert F, Haesebaert J, Zante E, Franck N (2020) Who maintains good mental health in a locked-down country? A French nationwide online survey of 11,391 participants. *Health Place* 66:102440
19. Hernandez-Fernandez F, Sandoval Valencia H, Barbella-Aponte RA, Collado-Jimenez R, Ayo-Martin O, Barrera C, Molina-Nuevo JD, Garcia-Garcia J, Lozano-Setien E, Alcahut-Rodriguez C, Martinez-Martin A, Sanchez-Lopez A, Segura T (2020) Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. *Brain* 143:3089–3103
20. Jacob L, Smith L, Koyanagi A, Oh H, Tanislav C, Shin JI, Konrad M, Kostev K (2021) Impact of the coronavirus 2019 (COVID-19) pandemic on anxiety diagnosis in general practices in Germany. *J Psychiatr Res* 143:528–533
21. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E,

- Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserre E (1996) Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 383:707–710
22. Joutel A, Vahedi K, Corpechot C, Troesch A, Chabriat H, Vayssière C, Cruaud C, Maciazek J, Weissenbach J, Bousser M-G, Bach J-F, Tournier-Lasserre E (1997) Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. *The Lancet* 350:1511–1515
  23. Kowalski G, Slebarska K (2022) Remote working and work effectiveness: a leader perspective. *Int J Environ Res Public Health* 19:153236
  24. Kwon B, Lee E-J, Park S, Lee JS, Lee MH, Jeong D, Lee D, Kwon HS, Chang D-I, Park J-H, Cha J-K, Heo JH, Sohn S-I, Kim D-E, Choi-Kwon S, Kim JS (2021) Long-term changes in post-stroke depression, emotional incontinence, and anger. *J Stroke* 23:263–272
  25. Leboyer M, Pelissolo A (2020) Psychiatric consequences of Covid-19 are in front of us. *Ann Med Psychol (Paris)* 178:669–671
  26. Mathieu S, Treloar A, Hawgood J, Ross V, Kolves K (2022) The role of unemployment, financial hardship, and economic recession on suicidal behaviors and interventions to mitigate their impact: a review. *Front Public Health* 10:907052
  27. Mengin A, Alle MC, Rolling J, Ligier F, Schroder C, Lalanne L, Berna F, Jardri R, Vaiva G, Geoffroy PA, Brunault P, Thibaut F, Chevance A, Giersch A (2020) Psychopathological consequences of confinement. *Encephale* 46:S43–S52
  28. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K (2020) Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. *Clin Neurol Neurosurg* 194:105921
  29. Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389
  30. Ozamiz-Etxebarria N, Dosal-Santamaria M, Picaza-Gorrochategui M, Idoiaga-Mondragon N (2020) Stress, anxiety, and depression levels in the initial stage of the COVID-19 outbreak in a population sample in the northern Spain. *Cad Saude Publica* 36:e00054020
  31. Patrono A, Invernizzi A, Placidi D, Cagna G, Calza S, Oppini M, Rechtman E, Papazaharias DM, Reichenberg A, Lucchini RG, Memo M, Ongaro E, Rota M, Wright RO, Renzetti S, Horton MK (2022) Impact of COVID-19-related social isolation on behavioral outcomes in young adults residing in Northern Italy. *Int J Environ Res Public Health* 19:1646
  32. Perneger TV, Combesure C, Courvoisier DS (2010) General population reference values for the French Version of the EuroQol EQ-5D health utility instrument. *Value in Health* 13:631–635
  33. Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y (2020) A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. *Gen Psychiatr* 33:e100213
  34. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, Zandi MS, Lewis G, David AS (2020) Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 7:611–627
  35. Rossi R, Succi V, Talevi D, Mensi S, Ntoliu C, Pacitti F, Di Marco A, Rossi A, Siracusano A, Di Lorenzo G (2020) COVID-19 pandemic and lockdown measures impact on mental health among the general population in Italy. *Front Psychiatry* 11:790
  36. Salari N, Hosseini-Far A, Jalali R, Vaisi-Raygani A, Rasoulpoor S, Mohammadi M, Rasoulpoor S, Khaledi-Paveh B (2020) Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. *Global Health* 16:57
  37. Santini ZI, Jose PE, York Cornwell E, Koyanagi A, Nielsen L, Hinrichsen C, Meilstrup C, Madsen KR, Koushede V (2020) Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis. *Lancet Public Health* 5:e62–e70
  38. Snaith RP, Harrop FM, Newby DA, Teale C (1986) Grade scores of the Montgomery—Åsberg Depression and the Clinical Anxiety Scales. *Br J Psychiatry* 148:599–601
  39. Tan BYQ, Chew NWS, Lee GKH, Jing M, Goh Y, Yeo LLL, Zhang K, Chin HK, Ahmad A, Khan FA, Shanmugam GN, Chan BPL, Sunny S, Chandra B, Ong JY, Paliwal PR, Wong LYH, Sagayanathan R, Chen JT, Ng AYY, Teoh HL, Ho CS, Ho RC, Sharma VK (2020) Psychological impact of the COVID-19 pandemic on health care workers in Singapore. *Ann Intern Med* 173:317–320
  40. Trifan G, Hillmann M, Testai FD (2020) Acute stroke as the presenting symptom of SARS-CoV-2 infection in a young patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *J Stroke Cerebrovasc Dis* 29:105167
  41. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, Ho RC (2020) Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *Int J Environ Res Public Health* 17:1729
  42. Wang C, Pan R, Wan X, Tan Y, Xu L, McIntyre RS, Choo FN, Tran B, Ho R, Sharma VK, Ho C (2020) A longitudinal study on the mental health of general population during the COVID-19 epidemic in China. *Brain Behav Immun* 87:40–48
  43. Williams OH, Mohideen S, Sen A, Martinovic O, Hart J, Brex PA, Sztrihai LK (2020) Multiple internal border zone infarcts in a patient with COVID-19 and CADASIL. *J Neurol Sci* 416:116980
  44. Williams SN, Armitage CJ, Tampe T, Dienes K (2020) Public perceptions and experiences of social distancing and social isolation during the COVID-19 pandemic: a UK-based focus group study. *BMJ Open* 10:e039334
  45. Yan L, Gan Y, Ding X, Wu J, Duan H (2021) The relationship between perceived stress and emotional distress during the COVID-19 outbreak: Effects of boredom proneness and coping style. *J Anxiety Disord* 77:102328
  46. Zhang T, Hirsh E, Zandieh S, Rodricks MB (2020) COVID-19-associated acute multi-infarct encephalopathy in an asymptomatic CADASIL patient. *Neurocrit Care*. <https://doi.org/10.1007/s12028-020-01119-7>
  47. Zhang XR, Huang QM, Wang XM, Cheng X, Li ZH, Wang ZH, Zhong WF, Liu D, Shen D, Chen PL, Song WQ, Wu XB, Yang X, Mao C (2020) Prevalence of anxiety and depression symptoms, and association with epidemic-related factors during the epidemic period of COVID-19 among 123,768 workers in China: a large cross-sectional study. *J Affect Disord* 277:495–502