

UNIVERSITÉ DE NANTES

FACULTÉ DE MÉDECINE

Année : 2021

N°

THÈSE

pour le

DIPLOME D'ETAT DE DOCTEUR EN MEDECINE

ANESTHÉSIE - RÉANIMATION

par

Alice CHOPIN

Née le 07 Mai 1992 à Issy les Moulineaux

Présentée et soutenue publiquement le 20 Avril 2021

Long-term anxiety and depression symptoms in caregivers of patients with moderate to severe

Traumatic Brain Injury

Multicenter prospective cohort study

Président : Monsieur le Professeur Antoine ROQUILLY

Directeur de thèse : Dr Raphaël CINOTTI

ABSTRACT

Objective. To describe the epidemiology of anxiety and depression symptoms in caregivers of patients, 6 months after moderate to severe traumatic brain injury (TBI).

Design. Ancillary study of a multicentric prospective randomized-controlled trial in nine university hospital in France. The primary outcome was the prevalence of anxiety and depression symptoms in caregivers, measured with the Hospital Anxiety and Depression Scale (HADS), 6 months after the TBI. The secondary aim was the identification of the risk factors associated with anxiety-depression symptoms in caregivers.

Measurements and main results. From the 306 surviving patients of the COBI (COntinuous hyperosmolar therapy in traumatic Brain-Injured patients) study, 171 (56.3%) relatives were included, mostly women (80.7%), composed of spouses / husbands (47.7%) or parents (39%). Eighty-three (50.6%) relatives suffered from high levels of anxiety ($\text{HADS-A} \geq 11$) and 59 (34.9%) from high levels of depression ($\text{HADS-D} \geq 11$). There was no cross-over between anxiety and depression symptoms. In univariate analysis baseline severity (Glasgow Coma Scale ≤ 8 , 39.1% vs 25.9%, $p=0.093$) and episode of intracranial hypertension (44.2% vs 29.6%, $p=0.055$) were associated with symptoms of depressions in caregivers. No risk factors were independently associated with depression symptoms in multivariable analysis. In univariate analysis, good neurological recovery (Glasgow Outcome Score Extended (GOS-E) > 5 , 63.4% vs 40.9%, $p=0.0043$) and improved autonomy in activities of daily living (Katz index 53.6% vs 30.4%, $p=0.0397$) at 6-months were associated with anxiety symptoms. In multivariate analysis, only GOS-E at 6 months remained significantly associated with anxiety symptoms (OR 2.51, IC 95 [1.33; 4.73], $p=0.0046$).

Conclusions. In this multicenter prospective cohort study, we identified a high prevalence of anxiety and depression symptoms among relatives of patients with TBI, at 6 months. Further research is needed to promote screening and psychological support strategies in caregivers.

Key Words: traumatic brain injury, relatives, anxiety, depression, ICU

RESUME

Objectif. Décrire l'épidémiologie des troubles anxieux et dépressifs chez les proches de patients traumatisés crâniens, 6 mois après un traumatisme crânien modéré à sévère.

Matériel et méthode. Etude ancillaire d'une étude prospective multicentrique, randomisée, menée dans 9 CHU en France. Le critère de jugement principal était la prévalence des symptômes anxieux et dépressifs chez les proches à 6 mois post-traumatique, évaluée par l'échelle HADS (Hospital Anxiety and Depression Scale). L'identification des facteurs de risque constituait le critère de jugement secondaire.

Résultats. Sur les 306 patients survivants de l'étude COBI, 171 proches (56.3%) ont été inclus, principalement de sexe féminin (80.7%), époux (47.7%), ou parents (39%). Quarante-vingt trois proches (50.6%) souffraient de niveaux significativement élevés d'anxiété (score HADS-A ≥ 11) et 59 proches (34.9%) de niveaux élevés de dépression (HADS-D ≥ 11). Il n'y avait pas d'interrelation entre les symptômes d'anxiété et de dépression. En analyse univariée les symptômes dépressifs étaient associés au score de Glasgow à l'arrivée (GCS ≤ 8 , 39.1% vs 25.9%, $p=0.093$) et à la survenue d'épisodes d'hypertension intracrânienne (44.2% vs 29.6%, $p=0.055$). Aucun facteur de risque ne restait significatif en analyse multivariée. Les symptômes d'anxiété étaient significativement augmentés en cas de bonne récupération neurologique à 6 mois (Glasgow Outcome Score Extended >5 , 63.4% vs 40.9%, $p=0.0043$) et de récupération d'autonomie dans la vie quotidienne (index de Katz = 6 (53.6% vs 30.4%, $p=0.0397$) en analyse univariée. En analyse multivariée, seul le GOS-E restait significativement associé aux troubles anxieux (OR 2.51, IC 95 [1.33; 4.73], $p=0.0046$).

Conclusion. Dans cette étude de cohorte prospective multicentrique, nous avons mis en évidence une forte prévalence de symptômes anxieux et dépressifs chez les proches de patients traumatisés crâniens modérés à sévères à 6 mois. Des études supplémentaires sont nécessaires pour promouvoir la mise en place de stratégies de dépistage et de prise en charge psychologique chez les proches.

Mots clefs : traumatisme crânien, proche, anxiété, dépression, réanimation

REMERCIEMENTS

À Monsieur le Professeur Roquilly, merci de l'honneur que vous me faites de présider ce jury.

Merci pour vos précieux enseignements, votre engagement dans la formation des internes. Merci pour les conseils éclairés, votre disponibilité et votre soutien tout au long de mon internat. Veuillez trouver ici l'expression de mon profond respect et de ma gratitude.

À mon Directeur de thèse, le Docteur Cinotti, sans qui ce travail n'aurait abouti. Merci de m'avoir accompagnée tout au long de cette rédaction. Soyez assuré de ma reconnaissance et de mon respect.

À Madame le Professeur Perrouin Verbe, vous me faites l'honneur de prendre part à ce jury.

Merci de l'expérience et du regard différent que vous amenez à cette thèse d'anesthésie-réanimation. Soyez assurée de ma reconnaissance et de mon respect.

À Monsieur le Professeur Asehnoune, merci de l'honneur que vous me faites de participer à ce jury. Merci de vos enseignements tout au long de cet internat. Soyez assuré de ma reconnaissance et de mon profond respect.

Au Docteur Le Courtois du Manoir, merci de l'honneur que vous me faites de participer à ce jury.

Merci pour les précieux conseils, l'accompagnement durant ces 6 mois de sénorisation au bloc des urgences, pour le plaisir de travailler à vos côtés au quotidien. Veuillez recevoir ma profonde reconnaissance.

A Céline Lerebourg, pour le soutien psychologique, la présence, les encouragements mutuels et pour tout le travail fourni tout au long de l'étude COBI.

A l'ensemble du personnel médical et paramédical qui a encadré ces onze années de médecine, de la PACES à Tours à la fin de l'internat Nantais ...

Aux **Professeurs Perrotin et Dequin** ainsi qu'à toute l'équipe de réanimation médicale du CHU de Tours pour m'avoir donné le goût de la réa... Merci de m'avoir encouragée à prendre cette voie.

Au **Professeur Destrieux** pour votre encadrement et votre franc-parler, vos cours d'anatomie mémorables et l'initiation à l'étude des fibres blanches cérébrales.

Au **Docteur Journaud**, alias Maëlle la meilleure interne, pour avoir égayé le début de l'externat et nous avoir chouchouté comme tu l'as fait. Je crois que tu peux être fière de tes pioupious!

À tous les médecins et internes qui ont rythmé 5 années d'internat,

De la découverte de l'anesthésie au bloc de neurochirurgie et à l'ICO Gauducheau; Merci à toute l'équipe de Gauducheau pour gentillesse et votre encadrement. Revenir remplacer chez vous aura été un plaisir, merci pour l'ambiance « Bisounours » toujours présente.

Par la suite l'arrivée au PTMC pour ces 6 mois au bloc d'uro-dig et à la maternité, merci à l'ensemble des médecins, IADES, et vieux internes, qui m'ont tant appris.

Du premier stage de Réanimation au cours de ces 6 mois en réanimation polyvalente à l'HGRL, merci au Dr Lakahl pour son hommage musical à Johnny Hallyday et pour avoir su me dire les choses quand il fallait, au Dr AmbrosiX pour ses œuvres d'art du haut du 2ème étage vue place Graslin, à tous les IDE (mention spéciale pour l'équipe de nuit, le blanc manger coco, le patin en poum-poum short) et au reste de l'équipe médicale. Merci à cette super équipe de co-internes,

Cécile, Jules, Matthieu, pour avoir égayé ces 6 mois, si bien staffé ma vie sentimentale (ou pas) et pour m'empêcher d'oublier le pipi-terrasse

Du semestre d'été en Réa med', une belle bande de co-internes et un semestre formateur. Merci à l'équipe médicale pour votre rigueur, vos connaissances, pour apporter chacun votre spécificité à ce service. Merci aux paramed' pour votre soutien lors des longues nuits de garde, pour les biscottes et le gel d'écho.. Pensée à ***Alice***, co-interne de choc et partenaire de soirées pas toujours réussies.

De la découverte de la périph' avec ce bel hiver à La Roche sur Yon, merci à toute l'équipe médicale pour votre gentillesse et vos connaissances, l'apprentissage de l'ALR, la bonne ambiance.

Du retour au CHU dans le monde merveilleux de la pédiatrie.. Merci à l'équipe d'anesthésistes pour votre rigueur, merci à toute l'équipe d'IADES pour votre gentillesse et votre bonne humeur, votre accueil, pour avoir supporté mes râleries (aaaah, la pédia et moi, un grand amour) et pour les foulées du tram' avec vous !

Puis la découverte de la chirurgie cardiaque, un été en CTCV.. Merci à toute l'équipe de chirurgiens, anesthésistes, IADES, IBODES, pour m'avoir fait tant apprécier cette spécialité. Merci à ***Hugo***, co-interne au top, pour les gouters au soleil, les bières après le bloc et pour avoir animé les trajets du matin ! A l'équipe de co-internes de la Réa, spéciale dédicace à ***Jules et Alexiane***, pour tous les bons moments qui ont suivi. Un grand Merci au Pr Rozec, pour votre soutien dans mes démarches au long de l'internat, pour vos conseils.

Un hiver à Grenoble, comment oublier ? Un semestre riche sur tous les plans, médical, sportif, sentimental.. Merci à toute l'équipe du déchocage pour avoir confirmé mon amour de la traumatologie, pour votre encadrement et votre rigueur. Merci à l'équipe de l'internat, particulièrement à Eric et

Louise, pour vos petites attention au quotidien. Merci à l'équipe médicale et paramédicale de RPC
Et surtout Merci à ceux qui m'ont entouré durant ces 6 mois, pour tous les bons moments autour
d'un verre ou sur des lattes, **Pauline, Raïa, Inès, Cédric et la team de l'Astro, Martin, Giovanni, Diana** .. Et à ma **Elo**, merci pour tout ! Rendez vous à Montpellier ou à Annecy.

De la réanimation chirurgicale au CHU, sacré semestre.. Merci à toute l'équipe de médecins pour
votre patience, vos connaissances, votre humour et tous vos conseils. Merci pour ces mots en fin de
stage qui me touchent encore. Merci à mes co-internes d'avoir supporté mes humeurs, **Côme** pour ta
gentillesse et les rires au quotidien, aux copines devenues amies **Pauline et Leïla**. Merci les filles
pour votre présence, votre soutien, pour tous ces bons moments ensemble. Je vous souhaite le
meilleur. Hâte de vous revoir dans « mes montagnes »!

De la séniorisation, l'entrée dans la cour des grands, au sein du bloc des urgences.. Merci à toute
l'équipe, anesthésistes, IADES, IBODES, IDE, AS. Un bonheur de travailler avec vous au
quotidien. Merci à l'ensemble des anesthésistes, qui savent si bien transmettre et entourer, former.
Travailler à vos côtés est un honneur et une chance, la séniorisation chez vous ça fait grandir ! Ce
semestre restera un des meilleurs souvenirs de mon internat.

Et enfin, un grand Merci aux équipes des **clinique Jules Verne à Nantes et Belledonne à Grenoble**
pour tous les bons moments chez vous. Merci de savoir si bien chouchouter les remplaçants !

Merci à tous ceux qui, médicaux ou non, ont rythmé ma vie durant ces 11 ans..

À Hannane, best externe of the world, je te souhaite de t'épanouir dans ton internat. J'attends
toujours de découvrir le Maroc à tes côtés !

À Amélie, Dr Hiard, pour tous les bons moments durant ce semestre ensemble. Pour m'avoir accueillie chez toi au sein de ta petite famille, comme je suis contente de t'y voir si épanouie.

À Marine, la copine du poney devenue brillante avocate. Je suis fière de toi, de ton parcours, Merci pour ton amitié qui a traversé les années et qui compte, bien que la vie nous ait éloignées.

À Laura, ou devrais-je dire Dr Cortes, pour nos retrouvailles trop rares mais si agréables. On part où la prochaine fois ? Je te souhaite le meilleur.

À Killyan pour avoir été le grand frère que je n'ai jamais eu, pour ta protection et ta bienveillance à mon égard. Que dieu bénisse la SNCF, Hungry Music, Rose Noire et les pharaons.

À Victoire, ma petite Victoire, pour les footings au Puy de Sancy ou autour de l'étang de La Roche, pour ta bonne humeur, ton amitié et ton soutien. Je te ferai monter sur des skis c'est promis.

À Cécile, pour ta présence tout au long de l'internat, pour Momo, les runnings, ton premier chasse neige et ces foutus kilomètres 36 à 42 ! Plein de bonheur vous trois, Clément, Sofa(-score) et toi.

À Raph', pour ton amitié si précieuse, tes paroles réconfortantes, les coups de téléphone et les footings à deux. Un bonheur de te voir enfin épanoui. Je te souhaite le meilleur, et qui sait, peut être un jour seras-tu mon IADE quelque part dans la montagne ?

À Etienne, pour avoir toujours été là, malgré les hauts et les (très) bas. Pour être un si fin psychologue et parce qu'avec tout le fric que je te dois pour les consult' tu pourrais te payer un paquet de chemises neuves... Je suis fière de ce qu'on est devenus au fil des années et je sais que tu es promis à un sacré brillant avenir. Pierre qui roule n'amasse pas mousse ...

À Marine. Que ça soit sur des skis à Megève, sur un paddle à Ramatuelle avec Momoche, en haut d'un building à Londres, à dompter des chèvres à l'Alpage, à boire du vin dans un bistrot Parisien, à prendre mille photos dans un parc de Croatie, en faceTime depuis mon canapé ou à manger des gaufrettes dans une voiture sous le déluge.. Merci pour ton amitié et ta présence depuis toutes ces années, elle vaut de l'or. Merci à Chris' et Tof' pour votre accueil, c'est chaque fois un bonheur. Rendez vous à l'Alpage cet été, à refaire le monde depuis ce petit paradis sur Terre.

À Virgile, mon Amour, Merci pour tout. Pour ta présence si précieuse au quotidien, ton soutien sans égal, pour supporter mes bougonneries et mon impatience, mes tocs et mes envies de courir sous la pluie, pour savoir me redonner le sourire en toutes circonstances, pour avoir rendu (moins in)supportables ces derniers mois loin de toi.. Cette fin d'internat signera bientôt pour nous un nouveau départ et je ne pourrais en être plus heureuse.

Françoise, Ambroise, Nuch, Ambre, merci de m'accueillir dans vos vies.

À Papou et Mémé pour votre amour et tous ces souvenirs heureux. Je sais que là où vous êtes vous serez fiers de moi.. Je pense à vous si souvent, vous me manquez énormément.

Dad, Mam, que dire ? Merci d'avoir toujours cru en moi, de votre soutien sans faille, votre présence, votre patience et votre bienveillance.. Dad, pour ton ouverture d'esprit, ton humour autant que ta psychorigidité, pour m'apprendre à apprécier les petits bonheurs de la vie. Mam, pour ta rigueur, ta ténacité au quotidien et pour avoir si bien tenu notre petite famille. J'ai conscience de mon immense chance. J'espère pouvoir vous rendre un jour autant que vous m'avez donné. Merci pour tout, je vous aime tant.

TABLE DES MATIERES

Abstract	2
Résumé	3
Remerciements	4
Introduction	11
Methods	12
Statistical analysis	14
Results	15
Discussion	17
Conclusion	19
Bibliography	20
Appendices	23
Abbreviations	38

INTRODUCTION

Traumatic Brain Injury (TBI) affects 50 million people worldwide annually and is a major cause of death and disability around the world, especially in young healthy individuals (1). TBI is thus a major public health problem, with growing economical burden and social cost estimated at 400 billion US \$ worldwide annually (2). Among survivors, almost 50% of the patients suffer from chronic disabilities: psychiatric troubles (anxiety and depression disorders, Post Traumatic Stress Syndrome (3)), chronic pain, motor impairment, behavioral and cognitive deficits (4). These chronic health issues lead to a loss of autonomy, social difficulties, job loss, need for supervision or assistance in daily activities (5). From the initial Intensive Care Unit (ICU) admission to rehabilitation and discharge at home, families of TBI patients are deeply impacted. The family response to critical illness has been well described, and is now called PostIntensive Care Syndrome-Family (6). This term refers to the adverse psychological outcomes experienced by the family of ICU patients, with up to 30% of family members developing post-traumatic stress symptoms (7) and more than 50% suffering from symptoms of anxiety or depression (8–10). After hospital discharge, several studies (11–13) suggest that close relatives of TBI patients are more likely to experience stress, anxiety, depression, burden and poor family functioning. However, there is a lack of data on the frequency and severity of anxiety-depressive troubles, and their associated risk factors in TBI patients' relatives. Many of the current published studies suffer from limitations: small sample sizes, lack of standardization of data collection, heterogeneity of the scales used (14), variable severity of TBI or single-center approach.

The aim of this study is to describe the epidemiology of anxiety and depression symptoms in relatives of survivors of moderate to severe traumatic brain injury. We hypothesized that a better understanding of the risk factors of psychological disorders in relatives of TBI survivors will help to design innovative medical or psychological support in relatives' care.

METHODS

This is an ancillary study of COBI (COntinuous hyperosmolar therapy in traumatic Brain-Injured patients) NCT03143751 (15).

Design of the COBI trial.

The COBI study is a prospective multicenter randomized-controlled trial assessing the efficiency of continuous hyperosmolar therapy to improve neurological outcome after moderate to severe TBI (open intervention, with blinded assessment of the neurological outcome). The study was conducted in neuro-intensive care units from 9 university hospitals in France. The study protocol was approved by the Institutional Review Board of Ile de France VIII (France) the 8th of May 2017 with trial registration NCT03143751. Written consent for participation was provided by patient's legal surrogate before enrollment. Patients who had recovered sufficient capacity to provide consent were asked to consent to continue in the trial up to 6 months after trauma.

Patients aged from 18 to 80 years old, admitted for a moderate (Glasgow Coma Scale 9-12) to severe (Glasgow Coma Scale 3-8) traumatic brain injury with abnormal CT scan, were included in the first 24 hours after admission. Patients were randomized to a standard care or a continuous hyperosmolar therapy group: continuous intravenous infusion of 20% NaCl for at least 48 hours and as long as deemed necessary to control intracranial pressure. Patients were followed-up at 3 and 6 months to assess the Extended Glasgow Outcome scale, the Katz Index of Independence in Activities of Daily Living (ADL). Follow-up was performed through telephone interviews conducted by a dedicated trained medical staff and a research nurse team: three trained assessors neither involved in patient recruitment nor aware of patient assignment performed the follow-up.

Relatives of TBI patients

From the 370 patients enrolled in the COBI study, 66 (21.5%) were dead at 6-months follow-up. Out of the 306 surviving patients, 171 relatives (56.3%) were included in this ancillary study. Relatives of patients who had died at 6 months were excluded, considering the anxiety and depressive disorders related to bereavement as a separate entity.

Relatives were identified as their closest person (spouse, parent, friend, child, ...), and gave consent to participate to their specific follow-up. Specific information on this ancillary study was provided to the patient's caregiver at the time of inclusion. Six months after TBI and during the patient's follow-up, the relative's written consent for participation was obtained. We centrally interrogated relatives to collect the symptoms of anxiety of depression and investigated risk factors.

Primary outcome

Anxiety and depression of caregivers were evaluated 6 months after TBI, using the Hospital Anxiety and Depression Scale (HADS)(16). The HADS questionnaire was sent by mail and completed by the closest relative. The version of HADS used for the study is available in **appendix**. The HADS questionnaire consists in 14 questions divided into 2 subscales: Anxiety subscale (HADS-A) and Depression subscale (HADS-D) both containing seven items scored on four points (0-3). Responses are categorized into a specific level of Depression (D) and anxiety (A) with scores of 0, 1, 2 or 3 where 0 = no symptoms and 3 = severe symptoms. For each subscale, a zero to seven score indicates normal levels of anxiety and depression (no symptomatology), 8-10 a doubtful symptomatology and a total score equal or greater than 11 a certain symptom of anxiety or depression.

Secondary outcome

We explored the risk factors linked with certain symptomatology of anxiety and depression (HADS ≥ 11). First, we explored whether relatives with a certain symptomatology of depression also displayed a certain symptomatology of anxiety. Then, we studied the impact of the intrinsic characteristics of relatives (gender, kind of relationship with TBI patient), patients (age, initial severity of TBI: Glasgow Coma Scale at admission, episode of intracranial hypertension), and the 6-month recovery (Glasgow Outcome Scale Extended GOS-E) and independence (ADL Katz index). A good neurological recovery was defined as GOS-E score 6 to 8, indicating upper moderate disability to good recovery. A GOS-E score, lower or equal to 5 indicated poor recovery,

ranging from lower moderate disability (GOS-E=5) to death (GOS-E=1). For autonomy, a score of 6 on the Katz index defined independence in the activities of daily living (17). We also evaluated the impact of extrinsic factors on anxiety and depression symptoms: treatment intervention (continuous osmotherapy or standard care) and ICU characteristics (open to visits 24 hours a day versus restricted time slots, presence of a dedicated room used for meetings with family members, psychological support for relatives). A specific model was developed for anxiety and depression symptoms.

STATISTICAL ANALYSIS

When describing data from the COBI trial, continuous data are expressed as mean ($\pm$ standard deviation) or median [interquartile] and compared with the Student t-test. Nominal data are expressed as N(%) and compared with the Chi2 test whenever appropriate. Scores of anxiety and depression in the HADS scale are described as median (interquartile) in case of absent symptomatology (score < 8), doubtful symptomatology (score of 8-10) and certain symptomatology (score $\geq$ 11). First, we compared the epidemiology of anxiety and depression symptoms, in caregivers of patients with moderate to severe TBI. Since the repartition of anxiety and depression symptoms were not the same in caregivers, we elaborated 2 specific predictive models of anxiety and depression symptoms. First, we performed a univariate analysis comparing the risk factors between caregivers with a certain anxiety/depression symptomatology ($\geq$ 11) and caregivers with a doubtful of absent symptomatology (score < 10). In this univariate analysis we compared intrinsic factors related to the patient's baseline condition (age, severity of TBI, in-ICU intra-cranial pressure treatment), the patient's recovery at 6-months (favorable vs unfavorable outcome assessed with the Glasgow Outcome Scale, the level of autonomy assessed with the ADL), extrinsic factors such as the in-ICU organization (24/7 opening or not, availability of a full-time psychologist) or the arm of randomization and finally the relationship of the caregiver (spouse/husband, kinship...). All variables with a p value < 0.2 were then kept in the multivariable logistic regression model to

predict a certain symptomatology of anxiety/depression. A backward selection of variables was performed. Risk factors are expressed with their Odds Ratio and Confidence Interval of 95%. P value < 0.05 are considered statistically significant.

RESULTS

TBI Patients

From November 2017 to February 2020, 370 patients with moderate-to-severe traumatic brain injury were randomized and followed-up during 6 months in the COBI study. We included 171 relatives of 171 survivors among these patients (**Figure 1**). One hundred thirty-six (79.5%) patients were male, with a median age of 43 [IQR 25-58]. Out of the 171 patients, 111 (67.8%) underwent severe TBI (Glasgow Coma Scale ≤ 8) and 42 (24.6%) had undergone an intra-cranial neurosurgery at admission. The complete description of the TBI patients at admission is provided in **Table 1**. Seventy-six (44%) patients displayed a favorable outcome (GOS-E score of 6 to 8) and 146 (86%) were independent for activities of daily living (Katz index = 6) at six months. Patients' characteristics at 6-months are reported in **Table 2**.

Relatives

Out of the 171 relatives, 138 (80.7%) were women. The sample was composed of spouses / husbands (47.7%), parents (39.0%), and non-spouse/non-parent caregivers (14.1%) including children, siblings, friends or other relationship (**Table 2**).

Primary outcome

Data were complete for 164 (96%) and 169 (99%) relatives regarding anxiety and depression subscale of the HADS score. Six months after trauma, half of the relatives (N=83, 50.6%) had a certain symptomatology of anxiety (HADS-A ≥ 11) and 59 (34.9%) suffered from a certain symptomatology of depression (HADS-D ≥ 11). Twenty-eight (17.1%) and 24 (14.2%) relatives did not show any symptoms of anxiety or depression respectively. Fifty-three (32.3%) and 86 (50.9%) relatives had borderline symptomatology of anxiety or depression respectively (**Table 3**).

Secondary outcome

Out of the 83 relatives with certain symptoms of anxiety, only 19 (23.1%) displayed a certain symptomatology of depression. Only 19 (33.3%) out of the 57 relatives with a symptomatology of depression displayed a synergic symptomatology of anxiety. Seventeen (73.9%) of relatives without any depressive symptoms however presented clinically significant level of anxiety. Since there was no major cross-over between the symptoms of anxiety and the symptoms of depression (**Table 4**), we developed 2 specific predictive models. In the univariate analysis, the baseline severity of TBI and intensity of intra-cranial pressure treatment were not associated with certain symptoms of anxiety. The in-ICU organization (open 24/7 and assistance with a psychologist) was also not associated with anxiety symptoms. Only the 6-months favorable neurological outcome (GOS-E >5 63.4% vs 40.9%, $p=0.0043$) and autonomy (ADL Katz = 6 53.6% vs 30.4%, $p=0.0397$) were associated with a certain symptomatology of anxiety. The univariate analysis of risk factors of anxiety is displayed in **Table 5**. In the multivariable model adjusted on ADL and arm of randomization, only the 6-month favorable GOS-E was independently associated with a certain symptomatology of anxiety (OR 2.51, IC 95 [1.33; 4.73], $p=0.0046$).

Regarding depressive symptoms, there was a trend towards a certain symptomatology in case of severe TBI (39.1% vs 25.9%, $p=0.093$), or in case of intra-cranial hypertension during the ICU stay of the patient (44.2% vs 29.6%, $p=0.055$). The poor neurological recovery (GOS-E ≤ 5) at 6 months (40.4% vs 28%, $p=0.0923$) and decreased autonomy of patients (50% vs 32.6%, $p=0.099$) showed a trend towards a certain symptomatology of depression (**Table 5**). The type of kinship or relationship, in-ICU organization (psychologist, opening 24/7) were not associated with anxiety and depression disorders (**Table 5**). In multivariable analysis no risk factors were associated with a certain symptomatology of depression. ICU characteristics are available in **supplemental data**.

Regarding extrinsic factors, there was no difference related to the arm of randomization. The adjusted odds ratio for anxiety and depression in the intervention group was respectively 0.93 (95% CI, 0.50 to 1.74, $p=0.82$) and 1.46 (95%CI, 0.76 to 2.82, $p=0.25$).

DISCUSSION

The present multicenter prospective cohort study provides data on the rate of Anxiety and Depression disorder in a large number of relatives of patients with moderate to severe TBI. At 6 months post injury, respectively 50.6% and 34.9% of the relatives suffered from relevant symptoms of anxiety and depression. It is interesting to note that there was no interdependence between the occurrence of anxiety and depressive symptoms, which supposed that they are two separate entities that do not affect relatives in the same way. These results are in line with Schönberger et al (12), who suggested a difference in risk factors and links between anxiety and depression. Our study supports the hypothesis that anxiety disorders are correlated with neurologic outcome at 6 months post trauma (neurological recovery: GOS-E, autonomy in activities of daily living: ADL), whereas depression disorders tend to be related to characteristics of TBI patient at admission (initial severity of head trauma) and during ICU stay (intracranial hypertension requiring a medical treatment).

These results are consistent with previous studies. Kreutzer et al (11) were the first to use validated questionnaires to measure caregivers' psychological distress, using the Brief Symptom Inventory in 1994 : 47% of family members, especially spouses, demonstrated significant levels of emotional distress in anxiety, depression and paranoid ideation. Wistanley (13), using the GHQ28 scale at 18 months post injury, found a prevalence of 50% for psychological distress, especially anxiety, insomnia, social dysfunction and somatic complains. Schönberger (12) and Kreutzer (16) found similar rates, using respectively HADS and Brief Symptom Inventory scales, with half of the relatives suffering from significant level of anxiety symptoms, and about 20% exceeded cutoff scores for depressive symptomatology. Others (18,19) report higher rates for depression disorder, suggesting that up to 48-60% of relatives of severe traumatic brain injured may experience significant depression. These numbers are considerably higher than in the general population, where the prevalence of anxiety and depression disorder is about 10% (20,21). In comparison to all these studies, our clinical trial gives the advantage to provide modern multicentric and large data on this

topic.

Our study supports the hypothesis that anxiety disorders are correlated with neurologic outcome at 6 months post trauma (neurological recovery: GOS-E, autonomy in activities of daily living: Katz index), whereas no predictive risk factors of depression were significantly retrieved.

In previous studies, predictive factors of relative psychological distress have been highlighted: post-traumatic neurobehavioral impairment of TBI survivor (23), emotional state or mood changes (12), restrictions in participation (including both occupational activities and independent living skills) or in communication (13,24,25), changes in injured individual's emotional state (5) are all associated with stress, burden, anxiety and depression. This may, in part, explain that scales measuring neurological recovery and autonomy in the acts of daily living are not sufficient to predict the occurrence of anxiety depression disorders. In most studies, women are most likely to display long-term symptoms of anxiety and depression, what is not found in our results, probably because women are highly predominant in our cohort. The relationship between the patient and the close relative was not associated with psychological troubles, which is consistent with the results suggested by some studies (5,11,26) and confirmed by the meta-analysis of Ennis et al (27).

Finally, the fact that we do not find any association between ICU characteristics and the occurrence of anxiety-depressive disorders is consistent with recent literature. Indeed, strategies of communication with family in or after the ICU (28), optimization of ICU organization to facilitate access to relative, information delivery or psychological support to relatives have been proposed to reduce intensity and the frequency of the PostIntensive Care Syndrome-Family and improve family satisfaction (6,28–30) but, with a few exceptions (31,32), most of the tested approaches have failed. Emotional distress of relatives in ICU is a multidimensional problem, which genesis seem to be hardly modulable by targeted external interventions.

Still, there is a need to identify specific tools helping to screen for those disorders (14). Although there are many other existing scales (SCL-90 : Symptom Checklist-90, BSI : Brief Symptom Inventory, Zung's Self-Rating Depression Scale, ...), we choose to use the HADS in this study

because of its simplicity, reliability and validity. Based on Bjelland et al (33) results, a cut-off of 8 is used to define caseness on each subscale, giving sensitivities and specificities of 0.80 for both. This review revealed that HADS, despite its simplicity and brevity, showed similar sensitivity and specificity as longer questionnaires like GHQ-28. Initially designed for healthy people, HADS was successfully used to assess symptoms of anxiety or depression in relatives of hospitalized patients (9) and then among TBI caregivers.

Several limitations must be underlined. First, the COBI study only included moderate to severe TBI, so the present results cannot be extrapolated to mild TBI. Second, emotional distress was measured using self-reported measure, and there is a possibility of response bias. Future studies should use clinical interview or hetero-assessment when possible. Third, interesting characteristics of relatives could have been collected: age, education level, religion, prior family health or history of psychiatric disorders. In future direction, it would be interesting to integrate other parameters correlated with anxiety and depression troubles of relatives, such as interdependence between patient and caregiver mental health (34) and protective factors : coping (35), resilience capacity (34,36). Finally, relatives of patients who died in intensive care were not interviewed. This choice refers to the fact that bereavement, especially in ICU, is a particular situation, associated with its own psychological consequences (28,37).

CONCLUSION

This multicenter prospective cohort study has provided robust information documenting the long-term issues faced by a large sample of moderate to severe TBI patients' relatives. Based on our high overall mid-to-long term prevalence of symptoms of anxiety and depression, clinicians should be encouraged to identify and manage these disorders. This information may be used to promote education of health professionals, implementation of guidelines, generalization of screening tests and psychological support.

BIBLIOGRAPHY

1. Deuschl G, Beghi E, Fazekas F, Varga T, Christoforidi KA, Sipido E, et al. The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. *Lancet Public Health*. 2020 Oct;5(10):e551–67.
2. Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol*. 2017 Dec;16(12):987–1048.
3. Bombardier CH, Fann JR, Temkin NR, Esselman PC, Barber J, Dikmen SS. Rates of major depressive disorder and clinical outcomes following traumatic brain injury. *JAMA*. 2010 May 19;303(19):1938–45.
4. Ruet A, Bayen E, Jourdan C, Ghout I, Meaude L, Lalanne A, et al. A Detailed Overview of Long-Term Outcomes in Severe Traumatic Brain Injury Eight Years Post-injury. *Front Neurol*. 2019;10:120.
5. Ponsford JL, Downing MG, Olver J, Ponsford M, Acher R, Carty M, et al. Longitudinal follow-up of patients with traumatic brain injury: outcome at two, five, and ten years post-injury. *J Neurotrauma*. 2014 Jan 1;31(1):64–77.
6. Schmidt M, Azoulay E. Having a loved one in the ICU: the forgotten family. *Curr Opin Crit Care*. 2012 Oct;18(5):540–7.
7. Azoulay E, Pochard F, Kentish-Barnes N, Chevret S, Aboab J, Adrie C, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med*. 2005 May 1;171(9):987–94.
8. Köse I, Zincircioğlu Ç, Öztürk YK, Çakmak M, Güldoğan EA, Demir HF, et al. Factors Affecting Anxiety and Depression Symptoms in Relatives of Intensive Care Unit Patients. *J Intensive Care Med*. 2016 Oct;31(9):611–7.
9. Pochard F, Azoulay E, Chevret S, Lemaire F, Hubert P, Canoui P, et al. Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. *Crit Care Med*. 2001 Oct;29(10):1893–7.
10. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome-family. *Crit Care Med*. 2012 Feb;40(2):618–24.
11. Kreutzer JS, Rapport LJ, Marwitz JH, Harrison-Felix C, Hart T, Glenn M, et al. Caregivers' well-being after traumatic brain injury: a multicenter prospective investigation. *Arch Phys Med Rehabil*. 2009 Jun;90(6):939–46.
12. Schönberger M, Ponsford J, Olver J, Ponsford M. A longitudinal study of family functioning after TBI and relatives' emotional status. *Neuropsychol Rehabil*. 2010 Dec;20(6):813–29.
13. Winstanley J, Simpson G, Tate R, Myles B. Early indicators and contributors to psychological distress in relatives during rehabilitation following severe traumatic brain injury: findings from the Brain Injury Outcomes Study. *J Head Trauma Rehabil*. 2006 Dec;21(6):453–66.
14. Depression and Stress Management for Caregivers of Traumatic Brain Injury Patients. 2019;7(1):6.
15. Roquilly A, Lasocki S, Moyer JD, Huet O, Perrigault PF, Dahyot-Fizel C, et al. COBI (COntinuous hyperosmolar therapy for traumatic Brain-Injured patients) trial protocol: a multicentre randomised open-label trial with blinded adjudication of primary outcome. *BMJ Open*. 2017 Sep 24;7(9):e018035.
16. Kreutzer JS, Gervasio AH, Camplair PS. Primary caregivers' psychological status and family functioning after traumatic brain injury. *Brain Inj*. 1994 Apr;8(3):197–210.

17. Katz S, Akpom CA. A Measure of Primary Sociobiological Functions. *Int J Health Serv* [Internet]. 1976 Jul [cited 2021 Mar 10];6(3):493–508
18. Douglas JM, Spellacy FJ. Correlates of depression in adults with severe traumatic brain injury and their carers. *Brain Inj*. 2000 Jan;14(1):71–88.
19. Rivera P, Elliott TR, Berry JW, Grant JS, Oswald K. Predictors of caregiver depression among community-residing families living with traumatic brain injury. *NeuroRehabilitation*. 2007;22(1):3–8.
20. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. *Sci Rep*. 2018 Feb 12;8(1):2861.
21. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl*. 2004;(420):21–7.
22. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* [Internet]. 2018 Nov [cited 2021 Mar 8];392(10159):1789–858.
23. Riley GA. Stress and depression in family carers following traumatic brain injury: the influence of beliefs about difficult behaviours. *Clin Rehabil*. 2007 Jan;21(1):82–8.
24. Chan J. Carers' perspective on respite for persons with acquired brain injury. *Int J Rehabil Res* [Internet]. 2007 Jun [cited 2021 Mar 3];30(2):137–46.
25. Anderson MI, Parmenter TR, Mok M. The relationship between neurobehavioural problems of severe traumatic brain injury (TBI), family functioning and the psychological well-being of the spouse/caregiver: path model analysis. *Brain Inj*. 2002 Sep;16(9):743–57.
26. Harris JK, Godfrey HP, Partridge FM, Knight RG. Caregiver depression following traumatic brain injury (TBI): a consequence of adverse effects on family members? *Brain Inj*. 2001 Mar;15(3):223–38.
27. Ennis N, Rosenbloom BN, Canzian S, Topolovec-Vranic J. Depression and anxiety in parent versus spouse caregivers of adult patients with traumatic brain injury: a systematic review. *Neuropsychol Rehabil*. 2013;23(1):1–18.
28. Kentish-Barnes N, Chevret S, Champigneulle B, Thirion M, Souppart V, Gilbert M, et al. Effect of a condolence letter on grief symptoms among relatives of patients who died in the ICU: a randomized clinical trial. *Intensive Care Med*. 2017 Apr;43(4):473–84.
29. Weber U, Johnson J, Anderson N, Knies AK, Nhundu B, Bautista C, et al. Dedicated Afternoon Rounds for ICU Patients' Families and Family Satisfaction With Care. *Crit Care Med*. 2018 Apr;46(4):602–11.
30. Barreto BB, Luz M, Rios MN de O, Lopes AA, Gusmao-Flores D. The impact of intensive care unit diaries on patients' and relatives' outcomes: a systematic review and meta-analysis. *Crit Care Lond Engl*. 2019 Dec 16;23(1):411.
31. Amass TH, Villa G, OMahony S, Badger JM, McFadden R, Walsh T, et al. Family Care Rituals in the ICU to Reduce Symptoms of Post-Traumatic Stress Disorder in Family Members-A Multicenter, Multinational, Before-and-After Intervention Trial. *Crit Care Med*. 2020 Feb;48(2):176–84.
32. Lautrette A, Darmon M, Megarbane B, Joly LM, Chevret S, Adrie C, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med*. 2007 Feb 1;356(5):469–78.

33. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res.* 2002 Feb;52(2):69–77.
34. Shaffer KM, Riklin E, Jacobs JM, Rosand J, Vranceanu A-M. Mindfulness and Coping Are Inversely Related to Psychiatric Symptoms in Patients and Informal Caregivers in the Neuroscience ICU: Implications for Clinical Care. *Crit Care Med.* 2016 Nov;44(11):2028–36.
35. Nadig N, Huff NG, Cox CE, Ford DW. Coping as a Multifaceted Construct: Associations With Psychological Outcomes Among Family Members of Mechanical Ventilation Survivors. *Crit Care Med.* 2016 Sep;44(9):1710–7.
36. Boniatti MM, RESILIENCE-ICU Group. May resilient family members of critically ill patients experience less caregiving burden? *Intensive Care Med.* 2021 Feb;47(2):244–5.
37. Siegel MD, Hayes E, Vanderwerker LC, Loseth DB, Prigerson HG. Psychiatric illness in the next of kin of patients who die in the intensive care unit. *Crit Care Med.* 2008 Jun;36(6):1722–8.

APPENDICES

Figure 1 – Flowchart

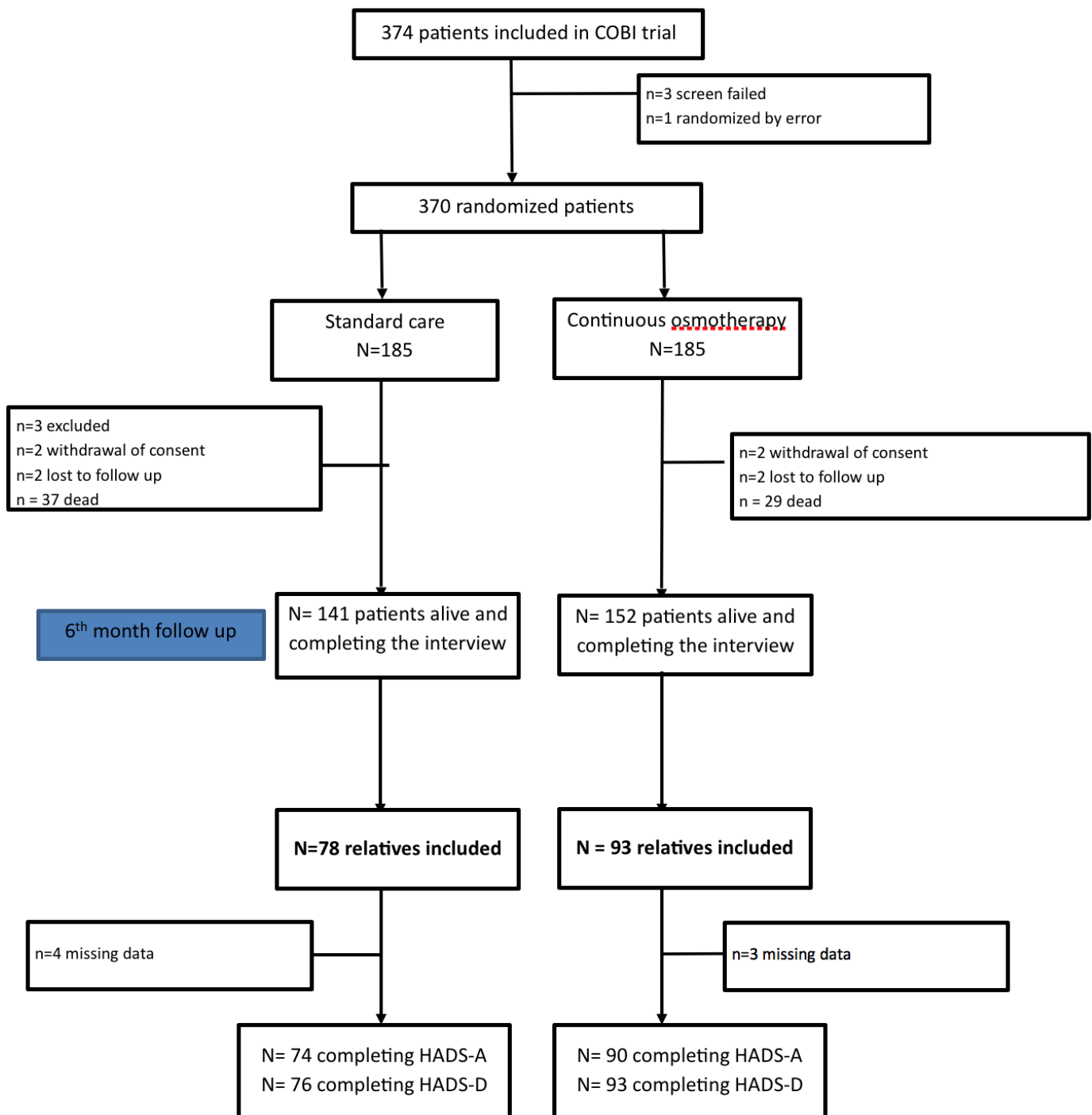


Table 1 – Baseline Characteristics of the Patients.

	Continuous hyperosmolar therapy group N=93	Control group N=78	Total N=171
Age (years) – median (25-75 th percentile)	40 (25-56)	44 (25-59)	43 (25-58)
Male – no. (%)	77 (82.8%)	59 (75.6%)	136 (79.5%)
Glasgow Coma Scale (GCS), median (25-75 th percentile),	8 (5-9)	7 (5-9)	7 (5-9)
Motor response ≤ 5 – no. (%)	83 (89.3%)	74 (94.9%)	157 (91.8%)
Severe traumatic brain injury – no. (%)	61 (65.6%)	55 (71.6%)	116 (67.8%)
Pupillary response – no. (%)			
Both reacting	66 (71%)	59 (75.6%)	125 (73.1%)
One reacting	19 (20.4%)	17 (21.8%)	36 (21%)
None reacting	8 (8.6%)	2 (2.6%)	10 (5.9%)
Hypotension – no. (%)	13 (14%)	12 (15.4%)	25 (14.6%)
Hypoxia – no. (%)	11 (11.8%)	7 (9%)	18 (10.5%)
Haemoglobin level < 9.0 g/L before randomisation	4 (4.3%)	6 (7.7%)	10 (5.9%)
Marshall CT classification – no. (%)			
I: Diffuse injury, no visible intracranial pathology	6 (6.5%)	2 (2.6%)	8 (4.7%)
II: Diffuse injury, midline shift of 0 to 5 mm	40 (43%)	38 (48.7%)	78 (45.6%)
III: Diffuse injury, basal cisterns compressed / effaced	9 (9.7%)	6 (7.7%)	15 (8.8%)
IV: Diffuse injury, midline shift >5 mm	3 (3.2%)	6 (7.7%)	9 (5.3%)
V: Evacuated mass lesion	27 (29%)	9 (11.5%)	36 (21%)
VI: Non-evacuated mass lesion	8 (8.6%)	17 (21.8%)	25 (14.6%)
Neurosurgery before randomisation, yes – no. (%)	28 (30.1%)	14 (18%)	42 (24.6%)
Decompressive craniectomy, yes – no (%)	7 (7.5%)	5 (6.4%)	12 (7%)

GCS: Glasgow Coma Scale

Severe traumatic brain injury: GCS ≤ 8

Hypotension: Systolic Blood Pressure <90 mm Hg before randomisation

Hypoxia: oxygen saturation <92% or PaO₂ < 10kPa before randomisation

Marshall CT classification: severity score based on the extent of brain damage on computed tomography, helps to quantify the severity of the brain damage and estimate the risk of developing intracranial hypertension

Table 2 – Characteristics of caregivers included at 6-months and the specific patients included in this ancillary study.

		Continuous hyperosmolar therapy group N=93	Control group N=78	Total N=171
ICU length of stay (days) - Median [IQR]		15 [9.00; 30.00]	17 [12.00; 32.0]	16 [10.00; 31.00]
Place of residence (N)	N	93	78	171
Hospital		26 (28%)	23 (29.5%)	49 (28.7%)
Discharged home		67 (72%)	55 (70.5%)	122 (71.3%)
Glasgow Outcome Scale-Extended (GOS- E) - 6 month				
Unfavorable outcome (GOS-E≤5) – no. (%)		51 (54.8%)	44 (56.4%)	95 (55.6%)
Favorable outcome (GOS-E>5) – no		42 (45.2%)	34 (43.6%)	76 (44.4%)
Activities of Daily Living (ADL Katz) - 6 month	N missing	0	1	1
Dependence (Katz > 6) - no. (%)		12 (12.9%)	12 (15.6%)	24 (14.1%)
Independence (Katz < 6) - no. (%)		81 (87.1%)	65 (84.4%)	146 (85.9%)
Relatives				
Male/female		11 (11.8%)/82 (88.2%)	22 (28.2%)/56 (71.8%)	33 (19.3%)/138 (80.7%)
Relationship with patients	N missing	0	1	1
Spouse		48 (51.6%)	33 (42.7%)	81 (47.6%)
Parent		35 (37.6%)	30 (39%)	65 (38.2%)

	Continuous hyperosmolar therapy group N=93	Control group N=78	Total N=171
Child	5 (5.4%)	7 (9.1%)	12 (7.1%)
Friend	1 (1.9%)	1 (1.3%)	2 (1.2%)
Sibling	2 (2.2%)	3 (3.9%)	5 (2.9%)
Sister	2 (2.2%)	1 (1.3%)	3 (1.8%)
Niece	0 (0%)	1 (1.3%)	1 (0.6%)
Cousin	0 (0%)	1 (1.3%)	1 (0.6%)

IQR: Inter Quartile Range

Table 3 - Anxiety and Depression symptoms in relatives of patients, 6 months after a TBI

	OSMOTHERAPY N=93	STANDARD N=78	Total N=171
HADS score - Anxiety			
N missing	3	4	7
Median [IQR]	11 [8–12]	11.00 [9–13]	11 [9–12]
Absence of symptomatology	17 (18.9%)	11 (14.9%)	28 (17.1%)
Doubtful symptomatology	28 (31.1%)	25 (33.8%)	53 (32.3%)
Certain symptomatology	45 (50%)	38 (51.4%)	83 (50.6%)
HADS score - Depression			
N missing	0	2	2
Median [IQR]	10 [8-11]	9 [8-11]	10 [8-11]
Absence of symptomatology	13 (14%)	11 (14.5%)	24 (14.2%)
Doubtful symptomatology	44 (47.3%)	42 (55.3%)	86 (50.9%)
Certain symptomatology	36 (38.7%)	23 (30.3%)	59 (34.9%)

Table 4 - Interdependence between anxiety and depression symptoms in caregiver of patients, 6months after a moderate to severe TBI.

	HADS depression		
	No symptomatology	Doubtful symptomatology	Certain symptomatology
HADS anxiety			
No symptomatology	2 (8.7%)	10 (12.2%)	15 (26.3%)
Doubtful symptomatology	4 (17.4%)	26 (31.7%)	23 (40.4%)
Certain symptomatology	17 (73.9%)	46 (56.1%)	19 (33.3%)

Chi2 Test $p=0.0071$

Table 5 – Univariate analysis of risk factors for Anxiety and Depression disorders

	ANXIETY Absence or doubtful HADS-A 0-10 N=81	ANXIETY Certain symptomatology HADS-A $\geq$ 11 N=83	p- value*
Relative relationship			
N missing	0	1	
Spouse/husband – no (%)	40 (51.3%)	38 (48.7%)	0.4985
Parent/child – no (%)	37 (50.7%)	36 (49.3%)	
Other – no (%)	4 (33.3%)	8 (66.7%)	
TBI patient characteristics			
Age			
Min-Max	18-77	18-74	0.6005
Average	43	42	
Glasgow score			
GCS $\leq$ 8 – no (%)	56 (49.1%)	58 (50.9%)	0.9176
GCS $>$ 8 – no (%)	25 (50.0%)	25 (50.0%)	
Need for high intra-cranial pressure treatment			
Yes – no (%)	29 (48.3%)	31 (51.7%)	0.8371
No – no (%)	52 (50.0%)	52 (50.0%)	
6 month outcome of TBI patient			
GOS-E			
Unfavorable outcome (GOS-E $\leq$ 5) – no (%)	55 (59.1%)	38 (40.9%)	0.0043
Favorable outcome (GOS-E $>$ 5) – no (%)	26 (36.6%)	45 (63.4%)	

	ANXIETY Absence or doubtful HADS-A 0-10 N=81	ANXIETY Certain symptomatology HADS-A $\geq$ 11 N=83	p- value*
Dependence (ADL Katz > 6)			
N missing	0	1	
Yes – no (%)	16 (69.6%)	7 (30.4%)	0.0397
No – no (%)	65 (46.4%)	75 (53.6%)	
ICU characteristics			
Full time equivalent (FTE) psychologist			
< 0.5 – no (%)	45 (50.0%)	45 (50.0%)	0.8632
0.5-1 – no (%)	36 (48.6%)	38 (51.4%)	
Open to families 24 hours a day			
No – no (%)	56 (49.6%)	57 (50.4%)	0.9491
Yes – no (%)	25 (49.0%)	26 (51.0%)	

	DEPRESSION Absence or doubtful HADS-D 0-10 N=81	DEPRESSION Certain symptomatology HADS-D $\geq$ 11 N=83	p- value*
Relative relationship			
N missing	0	1	
Spouse/husband – no (%)	51 (63.7%)	29 (36.3%)	0.6950
Parent/child – no (%)	52 (68.4%)	24 (31.6%)	
Other – no (%)	7 (58.3%)	5 (41.7%)	
TBI patient characteristics			
Age			
Min-Max	18-77	18-70	0.8206
Average	42.66	42.02	
Glasgow score			
GCS $\leq$ 8 – no (%)	70 (60.9%)	45 (39.1%)	0.0931
GCS $>$ 8 – no (%)	40 (74.1%)	14 (25.9%)	
Need for high intra-cranial pressure treatment			
Yes – no (%)	34 (55.74%)	27 (44.26%)	0.0553
No – no (%)	76 (70.37%)	32 (29.63%)	
6 month outcome of TBI patient			
GOS-E			
Unfavorable outcome (GOS-E $\leq$ 5) – no (%)	56 (59.6%)	38 (40.4%)	0.0923
Favorable outcome (GOS-E $>$ 5) – no (%)	54 (72%)	21 (28%)	
Dependence (ADL Katz $>$ 6)			
	0	1	

	DEPRESSION Absence or doubtful HADS-D 0-10 N=81	DEPRESSION Certain symptomatology HADS-D $\geq$ 11 N=83	p- value*
N missing			
Yes	12 (50%)	12 (50%)	0.0990
No	97 (67.4%)	47 (32.6%)	
ICU characteristics			
Full time equivalent (FTE) psychologist < 0.5	62 (66%)	32 (34%)	0.7908
0.5-1	48 (64%)	27 (36%)	
Open to families 24 hours a day			
No	73 (63.5%)	42 (36.5%)	0.5216
Yes	37 (68.5%)	17 (31.5%)	

Supplemental data - ICU characteristics

		Hyperosmolar therapy N=93	STANDARD N=78	Total N=171
	N	93	78	171
Full time equivalent (FTE) psychologist	<0.5	54 (58.1%)	42 (53.8%)	96 (56.1%)
	0.5-1	39 (41.9%)	36 (46.2%)	75 (43.9%)
Open to families 24 hours a day	No	62 (66.7%)	55 (70.5%)	117 (68.4%)
	Yes	31 (33.3%)	23 (29.5%)	54 (31.6%)
Room dedicated for family meetings	No	0 (0%)	0 (%)	0 (0%)
	Yes	93 (100%)	78 (100%)	171 (100%)

Appendix – French version of HADS questionnaire used for the study

Lisez chaque série de questions et cochez la case (une seule par question) correspondant à la réponse qui exprime le mieux ce que vous avez éprouvé au cours de la semaine qui vient de s'écouler.

Ne vous attardez pas sur la réponse à faire : votre réaction immédiate à chaque question fournira probablement une meilleure indication de ce que vous éprouvez qu'une réponse longuement méditée.

1. Je me sens tendu(e) ou énervé(e)

- | | |
|---------------------|--------------------------|
| La plupart du temps | ☐ |
| Souvent | ☐ |
| De temps en temps | ☐ |
| Jamais | ☐ |

2. Je prends plaisir aux mêmes choses qu'autrefois

- | | |
|------------------|--------------------------|
| Oui, tout autant | ☐ |
| Pas autant | ☐ |
| Un peu seulement | ☐ |
| Presque plus | ☐ |

3. J'ai une sensation de peur comme si quelque chose d'horrible allait m'arriver

- | | |
|-------------------------------------|--------------------------|
| Oui, très nettement | ☐ |
| Oui, mais ce n'est pas trop grave | ☐ |
| Un peu, mais cela ne m'inquiète pas | ☐ |
| Pas du tout | ☐ |

4. Je ris facilement et vois le bon côté des choses

- | | |
|-------------------------|--------------------------|
| Autant que par le passé | ☐ |
| Plus autant qu'avant | ☐ |
| Vraiment moins qu'avant | ☐ |
| Plus du tout | ☐ |

5. Je me fais du souci

- | | |
|---------------|--------------------------|
| Très souvent | ☐ |
| Assez souvent | ☐ |

- | | |
|------------------------|--------------------------|
| Occasionnellement | ☐ |
| Très occasionnellement | ☐ |
6. Je suis de bonne humeur
- | | |
|---------------------|--------------------------|
| Jamais | ☐ |
| Rarement | ☐ |
| Assez souvent | ☐ |
| La plupart du temps | ☐ |
7. Je peux rester tranquillement assis(e) à ne rien faire et me sentir décontracté(e)
- | | |
|------------------------|--------------------------|
| Oui, quoi qu'il arrive | ☐ |
| Oui, en général | ☐ |
| Rarement | ☐ |
| Jamais | ☐ |
8. J'ai l'impression de fonctionner au ralenti
- | | |
|------------------|--------------------------|
| Presque toujours | ☐ |
| Très souvent | ☐ |
| Parfois | ☐ |
| Jamais | ☐ |
9. J'éprouve des sensations de peur et j'ai l'estomac noué
- | | |
|---------------|--------------------------|
| Jamais | ☐ |
| Parfois | ☐ |
| Assez souvent | ☐ |
| Très souvent | ☐ |
10. Je ne m'intéresse plus à mon apparence
- | | |
|---|--------------------------|
| Plus du tout | ☐ |
| Je n'y accorde pas autant d'attention que je le devrais | ☐ |
| Il se peut que je n'y fasse plus autant attention | ☐ |
| J'y prête autant d'attention que par le passé | ☐ |
11. J'ai la bougeotte et n'arrive pas à tenir en

place

- | | |
|-------------------------------|--------------------------|
| Oui, c'est tout à fait le cas | ☐ |
| Un peu | ☐ |
| Pas tellement | ☐ |
| Pas du tout | ☐ |

12. Je me réjouis d'avance à l'idée de faire certaines choses

- | | |
|-----------------------|--------------------------|
| Autant qu'avant | ☐ |
| Un peu moins qu'avant | ☐ |
| Bien moins qu'avant | ☐ |
| Presque jamais | ☐ |

13. J'éprouve des sensations soudaines de panique

- | | |
|-----------------------|--------------------------|
| Vraiment très souvent | ☐ |
| Assez souvent | ☐ |
| Pas très souvent | ☐ |
| Jamais | ☐ |

14. Je peux prendre plaisir à un bon livre ou à une bonne émission radio ou de télévision

- | | |
|---------------|--------------------------|
| Souvent | ☐ |
| Parfois | ☐ |
| Rarement | ☐ |
| Très rarement | ☐ |

ABBREVIATIONS

ADL : Activities of Daily Living

BSI : Brief Symptom Inventory

CHU : Centre Hospitalier Universitaire

COBI : COntinuous hyperosmolar therapy in traumatic Brain-Injured patients

CT : Computerized tomography

FTE : Full Time Equivalent

GCS : Glasgow Coma Scale

GOS-E : Glasgow Outcome Scale – Extended

HADS : Hospital Anxiety and Depression Scale

ICH : Intracranial Hypertension

ICU : Intensive Care Unit

TBI : Traumatic Brain Injury

Thesis Title : Long-term anxiety and depression symptoms in caregivers of moderate to severe Traumatic Brain Injury patients

ABSTRACT

Traumatic Brain Injury (TBI) is a major cause of death and disability around the world, leading to chronic health issues, and families are deeply impacted. This prospective multicenter cohort study, ancillary of the randomized-controlled COBI trial, included 171 relatives of moderate to severe TBI patients, screened for anxiety and depression symptoms with the Hospital Anxiety and Depression Scale (HADS) at 6-months after the trauma. Risks factors were evaluated. Eighty-three (50.6%) of the closed relatives suffered from high levels of anxiety (HADS-A > 11) and 59 (34.9%) from high levels of depression (HADS-D >11). There was no interrelation between anxiety and depression, no correlation with relationship. Anxiety symptoms were significantly associated with patient's improved neurological outcome at 6 month, while depression symptoms tended to be associated with TBI initial severity but the association was not statistically significant in multivariable models.

KEY WORDS

Traumatic brain injury, relatives, anxiety, depression, ICU

Titre de Thèse : Symptômes d'anxiété et dépression à long terme chez les proches de patients traumatisés crâniens modérés à sévères

RESUME

Le traumatisme crânien (TC) est une cause majeure de décès et de handicap dans le monde, responsable de séquelles chroniques impactant les patients et leurs familles. Cette étude de cohorte prospective multicentrique, ancillaire de l'essai contrôlé randomisé COBI, a inclus 171 proches de patients ayant présenté un TC modéré à sévère, et évalué la prévalence des symptômes d'anxiété dépression à 6 mois via l'échelle HADS (Hospital Anxiety and Depression Subscale), et leurs facteurs de risque. Respectivement 83 (50.6%) et 59 (34.9%) patients souffraient de niveaux élevés d'anxiété et dépression (HADS-A et -D >11). Il n'y avait pas d'interdépendance entre les deux, pas de relation avec le lien de parenté. L'anxiété était significativement associée au bon devenir neurologique du patient à 6 mois (récupération, autonomie) et les symptômes dépressifs semblaient liés à la sévérité initiale du TC mais sans association statistiquement significative en analyse multivarée..

MOTS-CLES

Traumatisme crânien, proche, anxiété, dépression, réanimation