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Clinical paper

Memory performance, global cerebral volumes and hippocampal subfield volumes in long-term survivors of Out-of-Hospital Cardiac Arrest[☆]

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ABSTRACT

Aim: We explored the associations between global brain volumes, hippocampal subfield volumes and verbal memory performance in long-term survivors of out-of-hospital cardiac arrest (OHCA).
Methods: Three months after OHCA, survivors and healthy, age-matched controls were assessed with cerebral MRI and the California Verbal Learning Test-II (CVLT-II). Volumetric brain segmentation was performed automatically by FreeSurfer.
Results: Twenty-six OHCA survivors who were living independently in regular homes at the time of assessment and 19 controls participated in the study. Thirteen of the survivors had been conscious upon arrival to the emergency department. The other 13 survivors had 0.5–7 days of inpatient coma before recovery. Memory was poorer in the OHCA group that had been comatose beyond initial hospital admission compared to both other groups. Total cortical volumes, total hippocampus volumes and several hippocampal subfield volumes were significantly smaller in the OHCA group comatose beyond initial hospital admission compared to controls. No significant differences between the OHCA group conscious upon emergency department arrival and the other two groups were found for brain volumes. No significant differences were observed between any groups for white matter or total subcortical volumes. In OHCA survivors with recovery from inpatient coma, the various CVLT-II trials were significantly, but differentially, correlated to total gray matter volume, cortical volume and the hippocampal subfield subiculum.
Conclusion: In this small, single-site study, both hippocampal volume and cortical volume were smaller in good outcome OHCA survivors 3 months after resuscitation in comparison to healthy controls. Smaller cerebral volumes were correlated with poorer memory performance

Introduction

Out-of-hospital cardiac arrest (OHCA) can cause hypoxic-ischemic brain injury, which results in cognitive impairments in long-term survivors [1]. Impairments in declarative and episodic memory constitute an important characteristic of the cognitive profile after OHCA [1–3]. OHCA victims with such rapid recovery of consciousness that they are responsive within the time to admission to the emergency department have often been excluded from large research trials of long-term cognitive functioning [4–7]. It is assumed that this subgroup will show complete neurological recovery and better cognitive function compared to survivors who are unconscious longer [2,8,9]. A recent study by Sulzgruber et al., [9], largely contradicts this assumption. When performing a nuanced analysis of memory function in 33 survivors with good neurological outcomes four weeks after OHCA, survivors who were conscious upon admission to the emergency department showed the same difficulties on most memory tasks as those who had been unconscious upon arrival [9]. It has been questioned if the memory problems identified in this very rapid recovery group result from injury to the neurons that are extremely sensitive to hypoxic-ischemic insults [9,10]. The hippocampus has been targeted as one of the most vulnerable structures in animal studies, but evidence from humans is scarce [11]. The hippocampus, which plays an important role in episodic and declarative memory, is a heterogeneous structure that

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consists of several anatomically and functionally distinct subfields [12]. Whether distinct hippocampal subfields are differentially and selectively affected in adult, long-term, good outcome OHCA survivors or whether distinct subfields are heterogeneously related to verbal memory performance in this group has not been previously investigated [13].

Cerebral MRI with volumetric segmentation has rarely been utilized in the study of cognitive functioning in long-term OHCA survivors, which may be partly due to the large number of survivors with implanted internal cardiac defibrillators (ICD), which prevent assessment with MRI [14]. Literature searches performed for the past 20 years identified only two such studies with homogenous groups of survivors of cardiac arrest of a predominantly cardiac origin [14,15]. None of these studies confirmed a correlation between global hippocampal volumes and memory although hippocampal volumes were smaller in survivors compared to controls. Another volumetric MRI study of memory functioning exists in which multiple causes of hypoxic events were considered together without isolating cardiac arrest survivors from survivors of other etiologies [11,14,16].

In the present study, we investigated the correlations between memory performance and brain volumes in long-term survivors of OHCA, after comparing demographic, clinical, cognitive and volumetric MRI data between survivors and a healthy control group. Consistent with Sulzgruber et al., [9], all survivors in the present study had recovered to a good outcome at the time of assessment. In

addition, half of the survivors in the present study were conscious upon arrival to the emergency department. We hypothesized to find poorer memory performance, less gray matter volume, and smaller hippocampal volumes in the OHCA group with some durations of in-patient coma [14,15]. The assessment was performed 3 months after resuscitation, as most recovery in cognitive functions is expected by this time point [1,4,17–19].

Methods

Study setting

The data collection was performed between 2010 and 2013 at the University Hospital of North Norway (UNN-HF) in Tromsø as a part of a prospective cohort study with out-patient assessments of cognitive functioning 3 months after OHCA [3,19,20]. The UNN-HF is a tertiary hospital serving smaller hospitals in a regional manner. Every year, approximately 45 OHCA survivors are discharged alive from the cardiac ward. The hospital's protocols conform to current evidence-based guidelines for the advanced treatment and management of OHCA victims [21]. At the time of study recruitment, therapeutic hypothermia was included in the current treatment guidelines for OHCA victims who are comatose upon hospital arrival [22]. The current study did not involve any changes to the medical care for OHCA patients. Survivors were identified by cardiologists at the cardiac ward before discharge and later invited to participate in the study by mail. The study was approved by the Regional Committee for medical research ethics in Northern Norway (REK 2009/1395).

Research participants

Inclusion criteria were age between 18 and 85 years, first-time, normothermic OHCA due to a presumed cardiac cause. Only patients who were living independently in their regular homes without organized care at the time of follow-up were included and this criterion was used as the definition of a good outcome. Fluency in Norwegian language,normal hearing and vision were required. Previous cardiac arrest, a history of other neurological disease or traumatic brain injury, psychiatric disease or learning disabilities during formal education, ongoing severe somatic illness (e.g., cancer) or a psychological burden (e.g., moderate depression) at the time of assessment constituted the exclusion criteria. Survivors with ICDs, pacemakers or other body implants, not compatible with the magnetic environment, were not asked to attend the MRI assessment. Eligibility for study participation was determined through patient interviews and hospital record reviews. Medical data and resuscitation characteristics were obtained from the patients' hospital journals. Information regarding education and living situation were acquired from patient interviews.

The control group included age-matched volunteers recruited through advertising in the local newspaper. They reported no history of neurological, cardiovascular or psychiatric disorder. The procedure for the assessment of control participants was approved by the Regional Committee for medical research ethics in Northern Norway (2012/1588).

Sample size calculations

Sample size calculations were based on expected differences in memory performance between OHCA survivors and healthy controls. Controls were expected to perform similarly as the normative population mean (T-score mean = 50, SD = 10) and survivors significantly below ($T < 40$). With a desired power of 90% (1-β), and an alpha level of 0.05, a group size of 11 for both OHCA groups was needed to detect significant differences [23].

Memory assessment

Verbal memory was assessed with the standard version of the California Verbal Learning Test 2. edition (CVLT-II). Administration and scoring were performed according to standardized instructions [24]. The Norwegian translation was used [25]. The CVLT-II was administered as a part of a larger test battery reported in a previous publication [3].

The CVLT-II is a list-learning and recall task. The learning trial generates a total score from 5 separate recalls of a 16-item word list that is read aloud to the examinee who is to repeat the words from the list in random order after each reading. The test also includes a short-delay free recall trial and a long-delay recall trial, and both recall trials are to be performed with and without cues. The CVLT-II also includes a recognition trial and a forced choice trial. In the data analyses for the present study, we used the scores from the total learning trial, short- and long-delay free recall trials and recognition trial (not the cued recall trials or forced choice trial).

The raw scores obtained from the CVLT-II are converted to standardized scores using published normative data that correct for both age and sex [26].

Image acquisition and processing

The MRI assessment was performed after the memory assessment on the same day.

Subjects were scanned in a 1.5T Phillips Intera MR scanner using an 8-channel head coil. The T1-weighted structural scans were 3D turbo field echo scans with TR = 1825 ms, TI = 855 ms, TE = 4.0 ms, flip angle = 8°, and voxel resolution = $0.94 \times 0.94 \times 1.25\ mm^3$.

Volumetric segmentation of the T1 images was performed with FreeSurfer image analysis suite version 6.0. FreeSurfer involves an automated procedure for cortical reconstruction and volumetric segmentation [27]. The technical details are documented elsewhere [28], and the software is freely available for download online (http://surfer.nmr.mgh.harvard.edu/). FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths [29,30].

Hippocampal subfields were calculated by an automated segmentation process [31] implemented in FreeSurfer 6.0. In the present study, the volumetric data for the hippocampal subfields, estimated total intracranial volume (eTIV), total gray matter volume, total subcortical

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