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Postoperative cognitive dysfunction after liver transplantation

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ABSTRACT

Objective: Postoperative cognitive dysfunction (POCD) in liver transplant (LT) recipients is defined as a "more than expected" postoperative deterioration in cognitive domains, including short-term and long-term memory, mood, consciousness and circadian rhythm. It is diagnosed, after exclusion of other neurological complications, by using specific neuropsychological tests that need preoperative baseline. The aim of this systematic review was to assess the prevalence of POCD after LT and to analyze patients' symptoms, type and timing of assessment used.
Methods: PubMed, MEDLINE and The Cochrane Li-brary were searched up from January 1986 to August 2014. Study eligibility criteria are as follows: prospective and retrospective studies on human adult subjects describing prevalence of POCD and/or its sequelae after LT episodes were included.
Results: Eighteen studies were identified. The timing of testing for POCD may vary between different studies and within the single study, ranging from 0.5 to 32weeks. POCD occurs in up to 50% of LT recipient.
Conclusion: Future studies should be focused on detecting preoperative and intraoperative factors associated to POCD in order to carry out appropriate strategies aimed at reducing this disabling health condition. Relationship between POCD and long-term outcome needs to be investigated.

1. Introduction

Over the last decade, it has been highlighted that postoperative cognitive dysfunction (POCD) is a threatening complication and is independently associated with increased mortality in the first year after nontransplant surgery [1]. POCD, in the area of nontransplant surgery, is defined as an impairment of the mental processes of perception, memory and information processing occurring in the postoperative period [2]. It refers to the altered performance in two or more neuropsychological tests that investigate cognitive function measured as short-term or long-term memory and attention. It does not include the effect of residual sedation that, in the elderly, may persist long after the expected drug clearance [3]; also, postoperative delirium is a separate entity and may be diagnosed on the basis of clinical symptoms [4] and has been associated with early POCD [5]. In the area of noncardiac surgery, the POCD frequency seems to be around 20% among patients over 60years old [1]. The onset of POCD is most evident in the days immediately following surgery, with a maximum incidence around the seventh postoperative day. It may then persist for days or weeks, showing a tendency to shrink and eventually disappear beyond the third week after surgery, persisting at a distance of 1–2years in 1% of patients [1]. The higher incidence in old patients may be attributed to frequent deterioration of the general conditions, to the preexisting cerebrovascular disease and to a stronger sensitivity of the CNS [6]. Age > 60years is an independent risk factors associated with the development of POCD, together with preoperative hypertension and/or cardiovascular disease, preoperative mental impairment identified by the minimental state examination (MMSE) score less than 20, history of neurological or psychiatric diseases and chronic alcohol or drug abuse [6,7]. Other known risk factors for POCD occurrence include duration of surgery and postoperative infections [8–11]. Moreover, patients with longer hospital stays have been found to be more likely to exhibit POCD at hospital discharge [1]. It has been hypothesized that the deleterious effects of longer hospitalization on neurocognitive tests performance at hospital discharge may depend on sleep deprivation [1]. Interestingly, diabetes has not been identified as an independent risk factor [12].

Residual cognitive deficits are common immediately after liver transplant (LT) and it may depend on the extent of pretransplant morbidity [13–15]. Moreover, the possible persistence of some neurocognitive deficits within months, even in case of successful LT, raises the question of whether these deficits are completely reversible [15].

Neurological complications that may occur after LT, including embolic stroke, cerebral hemorrhage and central nervous system (CNS) infections, cause cognitive dysfunction of variable degree [15]. Differently from neurological complications, which are associated with a detectable damage in the CNS, POCD is a cognitive dysfunction diagnosed by specific tests after exclusion of other neurological complications. POCD has been attributed to several pathogenetic factors in LT

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recipients, such as comorbidities [14], poor graft function, recurrence of liver disease [13], anoxic and ischemic intraoperative damage, infections, immunosuppressant toxicity and metabolic and nutritional alterations. On the other hand, neuroinflammatory process in response to major surgery or infection seems to be the most recognized determinant factor for POCD, in the absence of other causes [16]. The aim of this systematic review was to assess the prevalence of POCD after LT and analyze patients' symptoms, in order to identify avoidable factors and appropriate strategies aimed at reducing this disabling health condition.

2. Methods

The literature search was conducted using computerized databases including PubMed, The Cochrane Li-brary and MEDLINE in order to identify the relevant articles that have been published from January 1986 to August 2014. Articles were retrieved using the following keywords: "postoperative cognitive dysfunction" AND "liver transplant", and "hepatic encephalopathy" and "cognitive function" and "transplant". Abstracts were read thoroughly before complete articles were obtained and the references from the relevant publications were manually explored to ascertain further potential articles. Inclusion criteria were human adult subjects, prevalence of POCD and/or cognitive sequelae and English language. Observational studies and retrospective analysis were not eliminated. Case reports/case series and review were not considered.

3. Results

Based on the search results, 61 titles and abstract were examined. A total of 45 articles did not met the inclusion criteria (20 review articles, 2 non-English manuscript, 1 nonhuman study, 3 nonadult study, 16 for lack of cognitive sequelae description, 1 living donor study, 2 case series). Another 3 relevant studies were identified through checking reference lists of the studies found to be eligible within the study. In the end, 19 publications were reviewed (see Table 1 for details).

3.1. POCD in LT recipients

The incidence and risk factors for POCD after LT have been poorly investigated. Some authors reported an incidence of POCD (44%) greater in LT recipients compared to other surgical populations [17]. They also have found a significant increase of serum C-reactive protein (CRP) and β-amyloid protein at 24h after surgery, in LT recipient with POCD [17]. The serum levels of these two biological markers correlate with the severity of cognitive impairment in Alzheimer's disease (AD) and other cognitive diseases [18,19]. This finding supports the hypothesis that POCD is due to a process similar to that seen in AD [20]. Some patients with POCD appear to exhibit a rapid aging in brain function that is similar to AD [21]. Rovira et al. used magnetic resonance imaging (MRI) to measure the volume of supratentorial focal brain white matter lesions and neuropsychological examination to assess cognitive function before LT as well as 6 and 14months after LT in 27 patients with cirrhosis without signs of hepatic encephalopathy (HE) [22]. These abnormalities, which are radiologically indistinguishable from the features of small-vessel disease of normal aging, were found to be partially reversible and parallel to the improvement of cognitive functions [23].

It has been demonstrated that patients with POCD had a greater severity of the hepatic illness before LT (model for end-stage liver disease score around 25) [17]. The authors also noted a more complicated surgical course, reflected by a large amount of blood transfused and a longer ventilation time, in those patients with POCD [17]. Moreover, the association between CRP and neurocognitive decline suggests the role of inflammation in the genesis of the POCD [24].

POCD in patients with liver disease is defined as a "more than expected" postoperative deterioration in cognitive domains, including short-term and long-term memory, mood, consciousness and circadian rhythm. It is diagnosed by specific neuropsychological tests, which are conducted before and after anesthesia. As delirium is the only specific sign of POCD, but it is not always present (see Table 2), preoperative assessment is mandatory. A higher incidence of delirium after nontransplant surgery has been found in patients with lower preoperative MMSE scores [1]. The decreased cognitive reserve (e.g., in patients with history of stroke), as a result of preexisting brain dysfunction, has been recognized as the main etiology of delirium in POCD patients [1]. In LT recipients, other factors may play a role in the etiology of delirium, such as inhibition of GABAErgic tone induced by calcineurin inhibitors (CIs), electrolyte, pH and osmotic disorders, systemic inflammation and infections [25].

LT recipients seem to be more vulnerable to neurological injury than other surgical patients [26]. It has also been suggested that a history of HE is associated with persisting neurological deficits 18months following LT [27], as measured after by the psychometric hepatic encephalopathy score (PHES) battery [27]. In patients with liver cirrhosis, the presence of preoperative HE seems to be an important risk factor for the persistence of cognitive deficits after LT [28,29]. Several previous studies have demonstrated substantial improvement in neuropsychological tests months to years after LT [22,30–34], especially for those patients with overt HE (OHE) [27], even if the return-to-normal value is less frequent [35]. The residual poor cognitive functions after LT in patients with previous HE could be attributed to a permanent structural component of HE that, contrary to the metabolic reversible component, persists regardless successful LT [28]. It has been reported that HE may cause brain damage, including neuronal loss, and animal models provide convincing evidence that several neuronal cell death mechanisms are activated in HE [36].

In patients awaiting LT without symptoms of OHE, preoperative neurocognitive tests may disclose the presence of minimal cognitive impairment so-called "minimal hepatic encephalopathy" (MHE). It is well know that MHE has high prevalence in patients with liver cirrhosis, ranging from 10% to 70% [28,29,22,37]. Instead, the prevalence of POCD across the studies ranges from 0% to 50% (see Table 1). The type cognitive assessment throughout the studies includes several components that are affected in MHE, such as attention, concentration, psychomotor speed and verbal and visuospatial short-term memory. Therefore, most of the studies consider also the persistence or worsening of preexisting cognitive deficits as POCD [27–29,22,37–42], in accordance with the statement that successful LT should remove HE [27,31,32].

MHE predicts OHE [43], but it is often clinically missed [44]. Some factor responsible for liver cirrhosis, such as hepatitis C virus (HCV) infection and, even more, alcohol abuse, can act as a confounder in MHE detection. Accurate screening for MHE in patients awaiting for LT may improve interpretation of cognitive disorders occurring after transplantation [25]. In fact, an incomplete reversal of preexisting cognitive dysfunction in patients with MHE after LT can occur [39]. Tarter et al. found a typical profile of MHE in 62 patients before LT was characterized by deficits of selective attention and fine motor skills, with spared general intellectual ability and, after LT, cognitive function was not completely restored [45]. Also Mattarozzi et al. observed that selective attention, visuospatial short-term and long-term memory and language tasks improved after 6months post-LT. Only selective attention continued to improve slightly, but significantly, until an 18-month assessment, whereas no other cognitive functions varied over time [34]. In a prospective study by Mechtcheriakov et al., a significant number of patients showed no improvement of the altered visuospatial and visuomotor abilities on average, retested around 21months after LT [39].

Neuroimaging studies support these results. On MRI, the typical hyperintensity T1-weighted pictures of basal ganglia, possibly due to manganese accumulation, seen in patients with cirrhosis decrease after LT but are still evident after 6months following the procedure [46].

Among cirrhosis-related factors, alcohol/drug abuse has been found to affect POCD occurrence [28]. Moreover, it has been hypothesized that brain damage resulting from chronic alcohol misuse and HCV infection