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Original article

Personalized risk prediction of postoperative cognitive impairment – rationale for the EU-funded BioCog project

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ABSTRACT

Postoperative cognitive impairment is among the most common medical complications associated with surgical interventions – particularly in elderly patients. In our aging society, it is an urgent medical need to determine preoperative individual risk prediction to allow more accurate cost–benefit decisions prior to elective surgeries. So far, risk prediction is mainly based on clinical parameters. However, these parameters only give a rough estimate of the individual risk. At present, there are no molecular or neuroimaging biomarkers available to improve risk prediction and little is known about the etiology and pathophysiology of this clinical condition. In this short review, we summarize the current state of knowledge and briefly present the recently started BioCog project (Biomarker Development for Postoperative Cognitive Impairment in the Elderly), which is funded by the European Union. It is the goal of this research and development (R&D) project, which involves academic and industry partners throughout Europe, to deliver a multivariate algorithm based on clinical assessments as well as molecular and neuroimaging biomarkers to overcome the currently unsatisfying situation.

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1. Background

Dementia-associated cognitive impairments result from different, interacting medical, physiological and molecular conditions (cognitive dysfunction with multifactorial etiology). Impaired cognition can be the consequence of age-associated primary brain disorders such as neurodegenerative conditions like Alzheimer dementia (AD) and/or cerebrovascular disease, depression, secondary brain disorders due to diabetes or other metabolic disorders, (chronic) inflammation, treatment interventions (e.g. anticholinergic drugs) as well as life style factors. An understanding of the interacting pathological mechanisms of cognitive impairment requires a cross-cutting "systems medicine" approach with different medical and scientific disciplines working together as well as studying different physiological and molecular mechanisms. This includes the application of molecular biomarker and neuroimaging technologies for stratification of cohorts. Supplementing traditional hypothesis-driven approaches, big data strategies using omics-platforms and bioinformatics tools may eventually help us to disentangle the complex interplay.

Postoperative cognitive impairment is a prime example of impaired cognition due to various reasons. One can think of it as a "quasi-experimental" model condition of cognitive decline with a well-defined starting point, i.e., the time point of surgical intervention, which is mostly planned ahead of time. Postoperative cognitive impairment is among the most common medical complications associated with surgical interventions – particularly in but not limited to elderly patients. In general, postoperative cognitive impairment is divided into two stages: (1) postoperative delirium (POD) (= delirium due to another medical condition, DSM-V: 293.0) and (2) postoperative cognitive dysfunction (POCD) (= major neurocognitive disorder due to another medical condition DSM-V: 294.10). During the acute and transient POD lasting hours and days after the surgical intervention, delirium can present either as hyperactive, hypoactive or mixed subtype. In rare cases POD can even persist. The hyperactive subtype presents with agitation, delusions and disorientation, which can be easily confused with psychosis in other neuropsychiatric conditions or it presents as hypoactive subtype. The latter is easily overlooked, apathy and quiet confusion are present and it can be confounded with depression. The incidence of POD after elective, non-cardiac surgery varies between 4–54% depending on a number of sociodemographic and clinical factors including age, duration of surgical intervention among others [1]. POD is frequently followed by the more chronic POCD which tends to persist over time [2,3]. In the ISPOCD1 study, the largest study of POD/POCD to date conducted during the early 1990s with funding from the European Union, $n = 948$ non-cardiac surgical patients were studied with preoperative cognitive assessment and follow-up investigations at 3 months. Cognitive decline was measured using a composite score of memory and/or attention tasks in a neuropsychological test battery. Cognitive decline occurred in 19% with no documented prior delirium, in 32% after short delirium duration (1–2 days), in 55% after prolonged delirium [2]. In elderly patients, POCD resembles dementia due to chronic neurodegeneration and appears to accelerate the cognitive decline in prior Alzheimer dementia [4]. In a recent meta-analysis [5], an odds ratio = 12.52 [95% CI, 1.86–84.21] was reported for the association of POD and the subsequent development of dementia after 3.2 and 5.0 years of follow-up (corrected for baseline dementia, severity of illness, age). A significant association between POD and mortality was also found after a mean follow-up of 11.4 months (OR = 1.71 [95% CI, 1.27–2.30]). In aging societies such as the western industrialized nations, the socioeconomic implications of postoperative cognitive impairments are therefore profound: POD/POCD are associated with longer and more costly hospital treatment, increased mortality, and dependency on social transfer payments [2]. Thus, developing effective diagnostic tools and treatments constitutes an urgent medical need – in particular, because there are hardly any treatments available partly due to a lack of understanding of the relevant pathological mechanisms. At present, the perhaps most important question to be clarified is it to establish diagnostic algorithms for the prediction of the individual (personal) risk to develop POD/POCD following a planned (elective) surgical intervention as part of a cost–benefit analysis prior to surgery. For instance, if a patient faces a high individual risk to develop cognitive impairments after surgery (e.g. hip replacement because of osteoarthritis or hip fracture), this patient may decide not to undergo surgery because the "costs" (cognitive impairment) are simply too high. Rather, this patient may opt for conservative treatment (long-term analgesic drug treatment). However, such a cost–benefit analysis would require an accurate algorithm for the prediction of POD/POCD, which is not yet available. The scale and urgency of this problem becomes even more obvious when considering the ongoing public discussion in the UK on hip replacement surgery, which is denied to thousands each year despite National Health Service (NHS) guidelines. Part of the problem is that these guidelines are rather vague in terms of cost–benefit analysis. The question who is going to develop cognitive impairment after surgery is not even part of the guidelines although expenses for surgery are generally not covered for older patients with preexisting cognitive impairment (dementia) since it is expected that these particular patients may not be able to cope with rehabilitation afterwards. At present, we are only able to make rough predictions on who is going to experience POD. Published prediction algorithms [6,7] are mostly based on older studies and the basis for prediction in these studies mostly relies on clinical studies with limited statistical power, which did not allow to address the question on possible interactions of risk factors – a major issue when one considers the multifactorial etiology of this condition. The Harvard group provided a long list of potential POD risk factors. However, for the most part, the individual risk due these factors was not further quantified due to an insufficient database. Even so, the group was able to attach a number at least to a few risk factors. On the basis of their work it is relatively safe to say that an approximately 2–3-fold increased risk for POD is seen in patients with preoperative age (> 70 years), impaired physical function, alcohol abuse, white blood count ($> 12{,}000$ cells/mm^3), hypo-albuminemia (< 3.5 g/dL) and clinical depression while the POD risk may even be higher in patients with preexisting cognitive impairment (Mini Mental State Examination Test [MMSE] < 24) – in fact, low MMSE scores have been most frequently reported as a POD risk factor. According to this study, plasma electrolyte concentrations and type of surgery may also play a quantifiable role (aortic vs. non-cardiac). Importantly, hardly any prediction is currently possible on who is developing (persisting) POCD, which is ultimately the more serious problem for a patient due to its tendency to become chronic. Originally, it was thought that POCD following POD is most likely to occur in elderly patients with preexisting cognitive impairment or clinically undetected preexisting neuropathology [3,6]. While this might be the case in a substantial portion of surgical patients, other factors may also play a considerable role like length of postsurgical Intensive Care Unit (ICU) stay, duration of delirium which itself partly depends on the duration (and the extent) of the surgical intervention [8,9]. Unfortunately, even though we know that these factors among others are risk factors for POCD, it is unclear how this translates into the individual (personal) risk of a patient. The scale of the problem becomes increasingly obvious. The trajectory of an initial decline (delirium) and subsequent prolonged impairment of cognitive function was highlighted by a recently published clinical study of Pandharipante et al. [10] in a mixed

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