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High-quality large-scale clinical studies on brain abscess : Finally !

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Among the 'big three' central nervous system (CNS) infections, brain abscess has long been neglected, in terms of research priority. Indeed, an unrestricted 'pubmed search' performed in December, 25th, 2021 retrieved 129,403 papers with the keyword 'meningitis', 72,336 with the keyword 'encephalitis', and 12,011 with the keywords 'brain abscess'. Not only the numbers of clinical research papers dealing with brain abscesses were small (10 times smaller than the number of papers dealing with meningitis), but they were mostly single-center and retrospective, so that their findings were often limited, and not generalizable. The reasons why brain abscesses have not stimulated much research efforts, until recently, remain unclear, but it may involve the followings: i) its low incidence, estimated at less than 1 per 100,000 inhabitants per year in developed countries (although close to that of encephalitis, which stimulated 6 times more papers); ii) the broad spectrum of micro-organisms potentially involved - including bacteria, fungi, and parasites; iii) its management by several medical specialties (i.e. infectious diseases, neurosurgery, microbiology, radiology, intensive care medicine, neurology, rehabilitation), with limited opportunities for trans-disciplinary research collaboration [1].

Fortunately, this situation has improved over recent years, under the leadership of colleagues from Northern Europe. A few years ago, Matthijs Brouwer *et al.* performed a systematic literature review and meta-analysis of almost 10,000 cases of brain abscess, to provide a large overview of clinical characteristics and outcome [2]. Thereafter, several landmark studies have been performed in Denmark, by a multidisciplinary consortium of researchers, to decipher the pathophysiology, the characteristics, and the outcome of brain abscess. These researchers took the opportunity of national registries with robust data, collected prospectively during several decades, about the health and the medical management of all people residing in the country. The combination of different nationwide prospective registries translated into reliable findings, based on clinically relevant scientific questions, well-designed statistical analyses, and large study population (5.8 million residents in Denmark). These invaluable tools were previously applied successfully for other severe infectious diseases, such as *Staphylococcus aureus* bacteremia [3]. For brain abscess, Jacob Bodilsen *et al.* provided the most robust data on outcomes available to date, with one-year mortality rate estimated at 21%, and a

prevalence of *de novo* epilepsy estimated at 32% in survivors [4]. They also identified the major risk factors for brain abscess through a large case-control study based on these prospective Danish registries, including data on 1,384 patients with brain abscess and 13,839 controls, and quantified the relative contribution of these risk factors. Accordingly, main contributors to the occurrence of brain abscess are neurosurgery (12%), solid cancer (11%), ear, nose, and throat infections (7%), and immunomodulating treatments (5%) [5].

In this issue of *Clinical Infectious Diseases*, the same consortium aimed to explore the link between oral health and brain abscess, and to evaluate the potential impact of invasive dental procedure on the risk of brain abscess (*Bodilsen J, Helweg-Larsen J, Otto Jarløv J et al. Dentist's visits and risk of brain abscess: A nationwide, population-based case control study. Clin Infect Dis* 2022). This time, they restricted the definition of cases to patients with culture-proven brain-abscess caused by oral cavity bacteria during years 1989-2016 (n=362), and selected 10 population controls per case, matched on age, sex, and residential area (n=3,257). They extracted data from four nationwide registries: i) the National Patients Registry, for information on all hospital admissions; ii) the Civil Registration System, for information on vital and migration status for all Danish residents; iii) the Danish National Health Service Register, for information on primary healthcare services, including dentist's visits; and iv) the healthcare records of all departments of clinical microbiology providing services to neurosurgical departments in Denmark, for information on the microbiology of brain abscess. They focused on two main exposures: i) invasive dental procedures performed within 6 months before the diagnosis of brain abscess, to estimate the risk associated with these procedures; ii) regular dentist's visits within one and three years before brain abscess diagnosis, as a proxy for good dental health.

The characteristics of patients with brain abscess included in this study is in line with literature data, with a median age of 53 years, and a male predominance (61%). Most common bacteria cultured from brain abscess samples were *Streptococcus* spp., *Fusobacterium* spp., *Haemophilus* spp., *Actinomyces* spp., *Prevotella* spp., and *Aggregatibacter* spp., all residents of the oral cavity, which confirms the validity of their inclusion criteria. However, they found no difference

in the proportion of invasive dental procedures during the six months before study inclusion between patients with brain abscess (21/362, 6%) and their matched population controls (179/3,257, 5%). Likewise, they found no difference in the frequency, and the patterns of dentist's visits within the three years prior to study inclusion. Several sensitivity and pre-specified subgroup analyses found no significant difference as well.

Where are we left with these unexpected findings? Firstly, these results should not be interpreted as a demonstration that dental health, and invasive dental procedures, have no role in the pathophysiology of brain abscess. Indeed, the study was observational – hence with potential biases, and may have been underpowered, despite its large scale, given the limited number of patients with culture-proven brain abscesses caused by oral cavity bacteria who underwent recent invasive dental procedures (n=21). Indeed, in their previous study on risk factors for brain abscess, with larger samples as it was not restricted to culture-positive brain abscesses, the same consortium found that previous in-hospital dental surgery was a risk factor for brain abscess, with an adjusted odds ratio of 2.57 (95% CI 1.71–3.84). Of note, this exposure was reported in only 2% of patients with brain abscess (22/1,384), and 0.3% of controls (40/13,839). Secondly, as elegantly suggested by the authors, both exposures analyzed may be associated with the risk of brain abscess in two opposite directions: Indeed, invasive dental procedures, or the number of dentist's visits, may both reflect either good care regarding dental health, or failure to prevent teeth diseases, which in turn would request more dentist's visits, and invasive dental procedures. These opposite associations may neutralize each other, with a final result suggesting no association. Thirdly, we may be grateful to the authors, and the editorial board of Clinical Infectious Diseases, for their commitment to publish these negative findings, despite our academic modern world tends to magnify positive results, and discard negative findings. Although the main findings of this study are negative, this paper is an important step ahead on our knowledge on brain abscesses. As the two other major CNS infections, brain abscesses are associated with a high burden of mortality, neurological sequels, and impaired quality of life. Robust data that will improve our understanding on the pathophysiology of this disease may allow to adjust preventive strategies.

How can we reconcile the facts that oral cavity bacteria are the most frequent micro-organisms identified in brain abscess samples [1][2], while only 6% of patients with brain-abscess caused by oral cavity bacteria underwent recent invasive dental procedures, and no association was found between proxy for dental health, and the risk of brain abscess? The primary reason may be that the risks of brain abscess related to everyday bacteremia in patients with healthy teeth, including bacteremia following toothbrushing [6], outweigh the risks associated with invasive dental procedures, and poor dental health. Hence, large population-based studies may not be adequate to identify the pathophysiology of brain abscess in these subgroups. Anyway, healthy teeth are obviously beneficial for the quality of life, and for the prevention of diseases much more common than brain abscess. The failure to demonstrate that it also decreases the risk of brain abscess should not decrease public health efforts to promote oral hygiene.

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NOTES

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