Journal of Clinical Neuroscience xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review article

The impact of transsphenoidal surgery on neurocognitive function: A systematic review

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ARTICLE INFO

Article history:
Received 20 October 2016
Accepted 22 January 2017
Available online xxxx

Keywords:
Pituitary tumors
Transsphenoidal surgery
Neurocognitive function

ABSTRACT

Background: Cognitive impairment following transsphenoidal surgery (TSS) among patients with pituitary tumors has been intermittently reported and is not well established. We performed a systematic review to summarize the impact of TSS on cognitive function.
Methods: We conducted a systematic search of the literature using the PubMed, Cochrane, and Embase databases through October 2014. Studies were selected if they reported cognitive status after surgery and included at least 10 adult patients with pituitary tumors undergoing either endoscopic or microscopic TSS.
Results: After removing 69 duplicates, 758 articles were identified, of which 24 were selected for full text review after screening titles and abstracts. After reviewing full texts, nine studies with a combined total of 682 patients were included in the final analysis. Eight studies were cross-sectional and one was longitudinal. These studies used a wide variety of neurocognitive tests to assess memory, attention and executive function post-operatively. Of the eight studies, six reported impairments in verbal and non-verbal memory post-operatively, while others found no association related to memory, and some reported an improvement in episodic, verbal, or logical memory. While four studies found an impaired association between TSS and attention or executive function, another four studies did not.
Conclusion: The current literature on cognitive impairments after TSS is limited and inconsistent. This review demonstrates that patients undergoing TSS may experience a variety of effects on executive function and memory post-operatively, but changes in verbal memory are most common.

1. Introduction

Pituitary tumors account for 10–15 percent of all intracranial tumors [1]. Neurocognitive impairment, specifically relating to memory and executive functioning, has previously been reported in patients harboring untreated pituitary tumors [2]. These impairments have been particularly associated with large lesions with suprasellar extension, which may obstruct the flow of cerebrospinal fluid and result in an increase in intracranial pressure [3]. Patients with pituitary tumors are at risk for a wide range of neurocognitive impairments, largely because the phenotypic behavior of these tumors can vary widely in terms of both size and hormonal status [1,4].

Transsphenoidal surgery (TSS) is widely considered surgical standard of care for pituitary tumors. Since the early 20th century, the use of endonasal TSS to access the sella for treatment of pituitary tumors has been widely practiced, primarily due to direct access and improved panoramic visualization of the ventral skull base [5]. The safety and clinical efficacy of TSS have been well established in patients with pituitary tumors [4–6].

Despite the overall efficacy of TSS, some studies have reported neurocognitive deficits post-operatively [3], while others have

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http://dx.doi.org/10.1016/j.jocn.2017.01.015
0967-5868/

found no such association [7]. Further complicating the picture of neurocognitive function in patients harboring pituitary tumors are the relatively common abnormalities in the pituitary and hypothalamic hormones, which may affect neurocognitive function directly, and inconsistencies in measuring cognitive function itself. Cognitive function tests that have been used in patients with pituitary tumors range widely, and include tests that evaluate memory (the Rey Auditory Verbal Learning Test [3,8], the Logical Memory Test [9,10], and the Recognition Memory Test [3,11]) or executive functioning and attention (the Digit Span Test [2,12], and the Trail Making Test [3,7,8,11,12]).

As a result of this large degree of heterogeneity, the effects of TSS on cognitive function among patients with pituitary tumors have not been well established in the current literature. In this study, we undertook a systematic review of the available evidence in the literature regarding the neurocognitive impact of TSS in patients harboring pituitary tumors.

2. Methods

2.1. Literature search

The PubMed, Cochrane, and Embase libraries were searched using relevant key words and medical subject headings to identify appropriate articles for inclusion according to the PRISMA criteria. The search strategy merged different search terms for TSS (e.g., neurosurgical procedures, neuroendoscopy, microsurgery), cognitive function (e.g., mental processes, memory, attention, executive function), and pituitary tumor (e.g., pituitary neoplasm, pituitary adenoma) by using several versions of special medical terms and text words. The detailed search elements are included in Appendix A. Reference lists of selected articles were examined to ensure that all relevant English-language articles published through October 2014 were identified.

2.2. Eligibility criteria and study selection

Studies were considered if they reported cognitive status post-operatively and included at least 10 adult patients with pituitary tumors undergoing either endoscopic or microscopic TSS. All titles and abstracts were screened, and potentially relevant articles were selected for full text screening. The full text screening was conducted independently by four authors (A.A., L.W., D.J.C., E.C.) and any disagreements were resolved by consultation with the senior author (T.R.S.).

2.3. Data extraction

The following information for each study was extracted using a standardized data extraction form: characteristics of the study (authors, publication year, country of origin, sample size, study design, journal impact factor), characteristics of participants (age, gender, inclusion/exclusion criteria, pituitary tumor types, hormone status and size), characteristics of the intervention (TSS type, time elapsed between surgery and cognitive testing, other types of neurosurgeries, number of patients who had TSS), and characteristics of the outcome (the type of cognitive tests, observations of each cognitive tests).

3. Results

3.1. Study characteristics

The initial search resulted in 827 English articles (244 from Pubmed, 581 from Embase, and 2 from the Cochrane Library). These articles were selected for title and abstract screening to determine whether they were appropriate for full text evaluation. A total of 24 articles were included for full text review and nine studies were included in this final systematic review (Fig. 1). A meta-analysis was not feasible due to the high heterogeneity across studies in included patients, tumor types, controls used, and tests used to measure neurocognitive function.

Characteristics of the nine included studies in the systematic review are found in Table 1. Seven were cross-sectional and two were prospective longitudinal. The mean age of participants ranged from 33.7 to 53 years. The total number of participants per study ranged from 14 to 148. All studies included both women and men. One study did not specify gender [13]. The female percentage varied between 34% and 82%. Three studies were conducted in the United Kingdom [3,10,13], two in the United States [9,11], two in the Netherlands [8,14], and two in Germany [7,12]. All studies included at least three different types of pituitary tumors except for three studies; two of which included only patients with Cushing's disease [8,9], and one that included only patients with non-functioning adenomas [14]. Study populations were compared against a variety of controls, including patients undergoing radiosurgery [10,11,14], transfrontal surgery [3], thyroid surgery [12], and healthy controls [8]. Two studies compared outcomes in the same patients pre- and post-operatively [7,9].

3.2. Memory

All studies included in this analysis reported at least one test that tapped the memory domain after TSS. Studies included multiple different memory tests: Auditory Verbal Learning Test, Wechsler Memory Scale, Recognition Memory Test, Logical Memory Test, and Verbal Memory Test. While some studies reported impairment in verbal and non-verbal memory [3,7,8,10,12,14], other studies found no association related to memory [7,9], or an improvement in episodic, verbal, or logical memory [14,15]. Verbal recall was impaired in several studies [3,7,8,12,14]. In a study by Mussig et al., one-third of TSS patients performed below average on the Auditory Verbal Learning Test [12]. In a study by Noad et al., 19 out of 71 reported patients fell below the 10th percentile in the Visual Memory Testing, and 14 out of 71 participants fell below the 10th percentile on the Logical Memory Test [10].

Regarding specific pituitary tumors, patients treated for Cushing's disease were reported to have a decline in both immediate and delayed recall on the Auditory Verbal Learning Test [8]. In a study by Starkman et al., 14 out of 23 patients treated for Cushing's disease with TSS showed improvement in logical memory recall [9]. Patients with nonfunctioning pituitary macroadenomas showed worse associative learning in the Wechsler Memory Scale than a control group that matched for age, gender, and education [8].

Only two studies examined pre- vs post-operative differences among the same patients [7,9]. Episodic memory was improved at 3 and 12 months post-operatively in these patients [7,9]. Verbal memory was improved 12 months post-operatively [7]. Two separate studies found no association between TSS and memory [11,14]. These studies largely compared outcomes between TSS and radiotherapy.

3.3. Attention and executive function

Studies included multiple different tests in the attention and executive function domains, including the Digit Span Test, Trail Making Test, Block Design, Ruff Figural Fluency Test, d2 Test of Attention, Digit Symbol Test, Stroop, and Verbal Fluency. Reported findings for attention and executive function in patients undergoing TSS for pituitary adenoma also varied widely. While some

Please cite this article in press as: Alsumali A et al. The impact of transsphenoidal surgery on neurocognitive function: A systematic review. J Clin Neurosci (2017), http://dx.doi.org/10.1016/j.jocn.2017.01.015