# Neuropsychological Outcome in Patients with Childhood Craniopharyngioma and Hypothalamic Involvement

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**Objective** To test memory performance and executive functions in patients with childhood craniopharyngioma and hypothalamic involvement.

**Study design** Using standardized neuropsychological tests, we compared cognitive performance in a group of 15 patients with childhood craniopharyngioma and known hypothalamic involvement and a group of 24 age- and intelligence-matched control subjects. In addition, we compared individual patients' results with normative data to detect abnormal performance in the clinically relevant range. Within the patient group, we further tested whether the grade of hypothalamic involvement had an impact on cognitive performance and quality of life.

**Results** Relative to healthy controls, the patients demonstrated significantly lower performance scores in tests of memory and executive functioning. On the individual performance level, delayed recall performance was severely impaired in one-third of the patients. Compared with patients with low-grade hypothalamic involvement, those with high-grade hypothalamic involvement showed worse performance in executive functions and reduced functional capabilities for daily life actions, indicating lower quality of life.

**Conclusion** Our findings demonstrate that hypothalamic involvement is related to impairments in memory and executive functioning in patients with childhood craniopharyngioma and indicate that a high grade of hypothalamic involvement is related to worse outcomes. *(J Pediatr 2014;164:876-81)*.

Craniopharyngiomas are rare epithelial tumors (accounting for 1.2%-4% of all childhood intracranial tumors) located within the sellar and/or parasellar region of the brain; 30%-50% are diagnosed during childhood and adolescence.[1] Although histologically benign, they often invade critical brain structures, such as the hypothalamus, including the mammillary bodies, the pituary gland, and the optic nerves.[2-4] Visual field defects and endocrine and neurobehavioral deficits are the most frequent sequelae of this tumor or its removal, with the potential for serious limitations in psychosocial functioning and quality of life.

Preoperative hypothalamic tumor involvement and postoperative hypothalamic surgical lesions have been identified as important predictors for long-term adverse outcomes in terms of obesity and diminished quality of life.[5-7] Cognitive sequelae have received less attention, and studies involving formal neuropsychological testing have reported conflicting results.[8-13] IQ has been shown to be within normal limits in the majority of studies.[8-11]

Previous studies investigating cognitive outcomes have used mixed samples not selected with respect to tumor and lesion site. The present study focused on cognitive functioning after craniopharyngioma removal by explicitly investigating a group of patients with known hypothalamic involvement. The patients' performance on a wide range of neuropsychological and psychological tests was compared with that of an age- and IQ-matched control group and with age-based normative data. In the patient group, we also tested whether the grade of hypothalamic involvement had an impact on cognitive performance and quality of life.

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|---|---|---|---|
| BMI | Body mass index | MRI | Magnetic resonance imaging |
| CANTAB | Cambridge Neuropsychological Test Automated Battery | PEDQOL | Pediatric Quality of Life Inventory |
| EORTC QLQ-C30 | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire | RVP | Rapid Visual Information Processing |
| | | SSP | Spatial Span |
| | | SWM | Spatial Working Memory |
| | | VLMT | Verbaler Lern- und Merkfähigkeitstest (German version of the Auditory Verbal Learning Test) |
| ESS | Epworth Sleepiness Scale | | |
| IED | Intra-Extra Dimensional Set Shift | | |
| MFI-20 | Multidimensional Fatigue Inventory | | |

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Given the role of the mammillary bodies in memory and the rich connections of the hypothalamus to frontal brain regions, we focused on memory and executive functioning. We hypothesized that patients with craniopharyngiomas, hypothalamic tumor involvement, and/or hypothalamic surgical lesions would demonstrate significantly lower test performance in both cognitive domains compared with the matched healthy control group.

## Methods

Patients were recruited from a group of individuals with a history of childhood craniopharyngioma. The sample included all patients (n = 200) who had been enrolled into the multinational, multicenter prospective surveillance studies of children and adolescents with craniopharyngioma (KRANIOPHARYNGEOM 2000/2007[1]) between 2001 and 2010. In addition, 1 patient from an older cross-sectional study (Hit-Endo[14]) with available data on hypothalamic involvement was included as well. The following eligibility criteria were applied to the 196 survivors (**Figure**; available at www.jpeds.com): hypothalamic tumor involvement/surgical lesion, no visual impairment that could interfere with task performance, and age at least 12 years at evaluation.

Because participants of the present study were also invited to participate in a functional magnetic resonance imaging (MRI) study during the same stay but on a different day (results will be reported elsewhere), we also verified their eligibility for MRI. The final sample included 15 patients (median age, 17.3 years; **Table I**). Participants in the healthy control group were selected to match the patient group with respect to age, sex, and intelligence. Their selection was based on a list of volunteers from other studies in our laboratory for whom results of previous IQ tests were available. The following eligibility criteria were applied for the control group: absence of known neurologic or psychiatric disorders, normal or corrected-to-normal vision, and normal hearing abilities (for both groups). The final control sample comprised 24 adolescents and young adults (median age, 17.6 years). The study was conducted in accordance with the Declaration of Helsinki, and all procedures were carried out with the adequate understanding and written consent of the participants or the primary caregivers of the adolescents. Ethics approval was obtained from the Ethics Committee of Carl von Ossietzky University, Oldenburg.

The general fluid ability of intelligence was assessed using the German adaptation of the Culture Fair Intelligence Test Scale II, short version.[15] Individual scores for state and trait anxiety were obtained with the German version of the State Trait Anxiety Inventory,[16] and a depression score was obtained with the German version of the Becks Depression Inventory.[17]

Information about patient history and current clinical status was obtained from clinical records of the KRANIOPHARYNGEOM 2000/2007 and Hit-Endo studies. To assess the current status of hypothalamic involvement, the most recent anatomic MRI images, all obtained after the last surgical or radiotherapeutic intervention, were assessed by a neuroradiologist who was blinded to the clinical data (M.W-M.). Patients were assigned to 1 of 3 grades based on a novel grading system for preoperative hypothalamic involvement/postoperative hypothalamic lesions (grade 0, no hypothalamic involvement/lesion; grade 1, involvement/lesion of the anterior hypothalamus, not involving the mammillary bodies and the hypothalamic area beyond the mammillary bodies; grade 2, hypothalamic involvement/lesion of the anterior and posterior hypothalamic area, involving the mammillary bodies and the area beyond the mammillary bodies).[6] Body mass index (BMI) was calculated for each subject at diagnosis and at study enrollment. Scores are reported as BMI SDS.[18] Based on Roth et al,[19] a BMI SDS >4 was defined as severe obesity; a BMI SDS of 2-4, as moderate obesity; and a BMI SDS <2, as normal weight.

Data related to health-related questionnaires were collected for the KRANIOPHARYNGEOM 2000/2007 studies for the patient group only. Functional capacities for recurrent activities of daily living were assessed using the Münster-Heidelberg Skills Rating Scale.[20] For self-assessment of quality of life, we used the recent German version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).[21] The German version of the Pediatric Quality of Life Inventory (PEDQOL)[22] was used in 4 adolescents for whom EORTC QLQ-C30 data were not available. Fatigue and subjective level of daytime sleepiness were assessed using the general fatigue scale of the Multidimensional Fatigue Inventory (MFI-20, German version)[23] and the German version of the Epworth Sleepiness Scale (ESS),[24] respectively. Detailed descriptions of these assessment tools are provided in the **Appendix** (available at www.jpeds.com).

The neuropsychological tests administered covered learning, memory, and executive functions and were validated for the complete age range of our sample. Participants were asked to complete the German version of the Auditory Verbal Learning Test (Verbaler Lern- und Merkfähigkeitstest [VLMT])[25] as a paper-and-pencil test, along with a series of 4 computerized tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition,

**Table I. Demographic and clinical characteristics of the control and patient groups**

| Characteristics | Controls | Patients | *P* value |
|---|---|---|---|
| Number | 24 | 15 | |
| Sex, male/female, n | 13/11 | 9/6 | .72 |
| Age, y, median (IQR) | 17.6 (4.8) | 17.3 (6) | .71 |
| IQ, median (IQR)* | 103 (20) | 101 (25) | .76 |
| Beck Depression Inventory, median (IQR) | 6 (8) | 5 (11) | .92 |
| Trait anxiety, median (IQR)† | 33.5 (10) | 33 (5) | .54 |
| State anxiety, median (IQR)† | 36 (13) | 33 (19) | .27 |

The $\chi^2$ test was used to test for possible between-group differences in sex, and the Mann-Whitney *U* test was used to test for between-group differences in all other variables. All tests were 2-sided.
*Assessed using the Culture Fair Intelligence Test II, short version.
†State-Trait Anxiety Inventory.