JNS

CLINICAL ARTICLE

J Neurosurg 128:1473–1478, 2018

Do craniopharyngioma molecular signatures correlate with clinical characteristics?

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OBJECTIVE Exome sequencing studies have recently demonstrated that papillary craniopharyngiomas (PCPs) and adamantinomatous craniopharyngiomas (ACPs) have distinct genetic origins, each primarily driven by mutually exclusive alterations: either *BRAF* (*V600E*), observed in 95% of PCPs, or *CTNNB1*, observed in 75%–96% of ACPs. How the presence of these molecular signatures, or their absence, correlates with clinical, radiographic, and outcome variables is unknown.

METHODS The pathology records for patients who underwent surgery for craniopharyngiomas between May 2000 and March 2015 at Weill Cornell Medical College were reviewed. Craniopharyngiomas were identified and classified as PCP or ACP. Patients were placed into 1 of 3 groups based on their genomic mutations: *BRAF* mutation only, *CTNNB1* mutation only, and tumors with neither of these mutations detected (not detected [ND]). Demographic, radiological, and clinical variables were collected, and their correlation with each genomic group was tested.

RESULTS Histology correlated strongly with mutation group. All *BRAF* tumors with mutations were PCPs, and all *CTNNB1* with mutations and ND tumors were ACPs. Preoperative and postoperative clinical symptoms and radiographic features did not correlate with any mutation group. There was a statistically significant relationship ($p = 0.0323$) between the age group (pediatric vs adult) and the mutation groups. The ND group tumors were more likely to involve the sella ($p = 0.0065$).

CONCLUSIONS The mutation signature in craniopharyngioma is highly predictive of histology. The subgroup of tumors in which these 2 mutations are not detected is more likely to occur in children, be located in the sella, and be of ACP histology.

https://thejns.org/doi/abs/10.3171/2017.1.JNS162232

KEY WORDS craniopharyngioma; *CTNNB1*; *BRAF*; papillary; adamantinomatous; pituitary surgery

Craniopharyngiomas are intracranial tumors that arise from embryonic remnants of Rathke's pouch in the craniopharyngeal duct.[9] Although classified as benign lesions, their invasive capacity and their presence in proximity to the optic apparatus, pituitary gland and stalk, third ventricle, and the hypothalamus are associated with progressive visual, hormonal, and neurological deficits and deterioration of quality of life as these tumors enlarge.[28]

The 2 classic subtypes of craniopharyngiomas, adamantinomatous (ACP) and papillary (PCP), have been classically considered similar lesions regarding their response to treatment. However, recent results of genetic and molecular studies have demonstrated important differences between them.[2–4,6,24,30,32] Exome sequencing studies have demonstrated that the tumors have distinct genetic origins, each mainly driven by mutually exclusive alterations in oncogenes. Recurrent mutations in *BRAF* (*V600E*), an

ABBREVIATIONS ACP = adamantinomatous craniopharyngioma; DI = diabetes insipidus; GTR = gross-total resection; ND = not detected; PCP = papillary craniopharyngioma.

SUBMITTED August 31, 2016. **ACCEPTED** January 26, 2017.

INCLUDE WHEN CITING Published online July 14, 2017; DOI: 10.3171/2017.1.JNS162232.

oncogene that regulates MAP kinase/ERK signaling and affects cell division and differentiation, has been observed in 95% of PCPs.[4] On the other hand, *CTNNB1* mutations, observed in 75%–96% of ACPs,[6,31] demonstrate that there is still a subgroup of tumors that do not fit this genetic-histological correlation. The understanding of these genetic characteristics may facilitate the pathological diagnosis of craniopharyngiomas and, specifically, guide clinical trials for the development of personalized medical treatments, such as the use of BRAF and MEK inhibitors for the management of PCPs.[2] However, in light of these new molecular definitions of craniopharyngiomas, several questions remain unanswered. There is a paucity of data on how the new molecular categories impact clinical presentation, including radiographic and endocrine features, anatomical location, and rates of gross-total resection (GTR) and recurrence. Moreover, the subgroup of patients with neither of the 2 mutations has not been closely examined. Finally, although pediatric patients almost uniformly harbor ACPs, it is not known whether the tumors all express the *CTNNB1* mutation or have no known mutation. In this study, we present a series of craniopharyngioma patients treated at our center and evaluate the correlation of genetic subtype and various clinical characteristics and results.

Methods

After receiving institutional review board approval, we reviewed the pathology database at Weill Cornell Medical College, NewYork-Presbyterian Hospital to identify patients who underwent surgery between May 2000 and March 2015 for histologically proven craniopharyngiomas. These tumors were profiled for driver mutations.

Patients were placed into 1 of 3 groups based on their genomic mutations: *BRAF* mutation only, *CTNNB1* mutation only, and tumors in which neither of these mutations was detected (not detected [ND]). These groups were compared with each other using clinical, radiological, surgical, and outcome parameters. Patients with inadequate follow-up information were excluded from the study (n = 5).

Patient Population

Fifty-one patients met inclusion criteria. The average age at the time of surgery was 9.7 years for pediatric patients (n = 8, range 5–16 years) and 50.1 years for adult patients (n = 43, range 19–88 years); 29 patients were female and 22 were male.

Preoperative Evaluation

Patients underwent preoperative clinical, laboratory, and radiological evaluation, and demographics, neurological examination, visual fields, and preoperative endocrine function data were examined. Blood samples were evaluated for prolactin, free thyroxine, fasting morning cortisol, insulin-like growth factor–1, testosterone, estrogen, follicle-stimulating hormone, luteinizing hormone, serum sodium, and urine-specific gravity. The radiological evaluation included contrast-enhanced CT scanning and MRI according to a neuronavigation protocol. Previous treatments were documented.

Radiographic Characterization

Tumor volume (calculated using the ABC/2 formula), location (existence of sellar tumor, suprasellar tumor, or ventricular tumor), and consistency (solid, cystic, or mixed) relative to mutation groups were analyzed.

Surgical Procedures

The most common approach to these tumors was the extended endonasal endoscopic approach (n = 42). The details of this surgical approach have been described previously.[19–21] Less commonly, a pterional or an orbitozygomatic approach was used to resect these lesions (n = 9).

Histology

Histological subgroups were reviewed by a neuropathologist (D.J.P.) who was blinded to the mutational status of the tumor. Thirty-nine patients had clear ACP histology, and 1 patient showed scant tumor consistent with ACP with an exuberant xanthogranulomatous response. Eleven patients had PCP histology.

Genetic Analysis

Sanger sequencing was performed for identification of known hotspot variants in the *CTNNB1* and *BRAF* genes. In a subset of cases (n = 9), mutational status was detected using a 50-gene next-generation sequencing panel that targets hotspots in cancer genes.

Outcome and Follow-Up

Patients underwent clinical, laboratory, and radiological evaluations throughout the hospital stay, and at 3 weeks, 6 weeks, 3 months, 6 months, 1 year, and every 2 years subsequently, for any new clinical features (CSF leakage, obesity, visual fields, hypopituitarism, diabetes insipidus [DI], tumor recurrence, or requirement of further treatment [e.g., reoperation, radiation]).

Statistical Analysis

Categorical data are reported as counts in each mutation group. Pearson's chi-square test was used to assess dependence with a simulated p value based on 2000 replicates; significance was set at $p < 0.05$. For distribution of age and the volume of tumors between mutation groups, ANOVA was used.

Results

Demographics

Of the 51 patients included in this study, the *CTNNB1* group was the largest group with 33 patients. The number of patients, average age, and sex distributions are summarized in Fig. 1A and B. There were no pediatric patients in the *BRAF* group, but they accounted for 43% of the ND group. There was a statistically significant relationship ($p = 0.0323$) between age group (pediatric [<18 years] vs adult [>18 years]) and the mutation groups. Sex and age were not significantly different.

Preoperative Visual and Endocrine Deficits

Vision was normal in 7 patients. Visual deficit was the

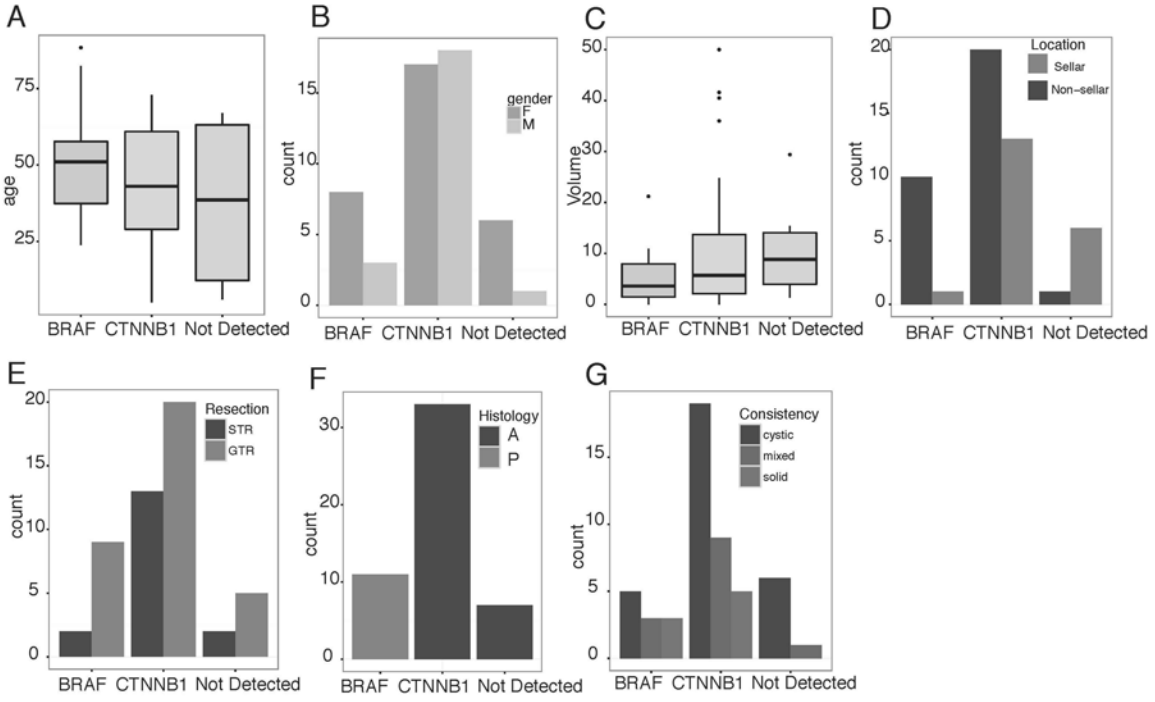

FIG. 1. Association of clinical features with mutational subgroups in patients with craniopharyngiomas. Distribution of age (**A**), sex (**B**), tumor volume (in cm^3) (**C**), tumor location (**D**), resection type (**E**), histological subtype (**F**), and tumor consistency (**G**). In the box and whisker plots (A and C), the *line* within the box indicates the median; the *box*, the interquartile range; the *vertical lines*, the entire range; and the *dots*, the outliers. A = ACP; P = PCP; STR = subtotal resection.

most common complaint and the most common neurological examination finding in both *BRAF* and *CTNNB1* groups. Pituitary insufficiency was the most common finding in the ND group (86%). No significant difference was observed between the groups.

Tumor Size and Radiographic Characteristics

The average tumor volume and sellar location relative to different mutation groups are summarized in Fig. 1C and D. Six (86%) of the 7 lesions in the ND group were located in and/or extending into the sellar cavity; however, only 1 lesion (9%) in the *BRAF* group had a sellar location ($p = 0.0065$). Tumor size varied between 2.0 and 50 cm^3 (mean 10.02 cm^3; 1 cystic tumor with a volume of 315 cm^3 was excluded). Tumor consistency is summarized in Table 1. Tumor size and consistency did not statistically significantly differ between mutation groups.

Extent of Resection and Recurrence

Of the 51 procedures, GTR was planned in 39 cases (10 [91%] of 11 in the *BRAF* group and 6 [86%] of 7 in the ND group, and 23 [70%] of 33 in the *CTNNB1* group) and was achieved in 36 cases (92%; 10 [91%] of 11 in the *BRAF* group, 21 [64%] of 33 in the *CTNNB1* group, and 5 [71%] of 7 in the ND group). There were no significant differences between groups in regard to GTR (Fig. IE).

Histology

All tumors in the *BRAF* group were PCPs, all tumors in the *CTNNB1* group were ACPs, and all tumors in the ND group were ACPs (1 exhibited scant tumor consistent with ACP features with an exuberant xanthogranulomatous response; $p = 0.0005$) (Fig. 1F).

Visual and Endocrine Outcome

The median follow-up duration was 89 months (range 3–180 months). Twenty-six patients had improved vision postoperatively, and 7 had a decline in vision. The visual outcomes did not differ significantly between groups. Forty-one patients either had or developed hypopituitarism (17 patients developed hypopituitarism postoperatively). Twenty patients had DI preoperatively, and 19 developed DI after surgery. The detailed data regarding endocrine outcome are presented in Table 2. All patients in the ND group had DI postoperatively. There was no significant difference between the groups in their presentation with hypopituitarism and/or DI or developing hypopituitarism and/or DI postoperatively (Table 2).

Complications

There were no perioperative deaths. The complication rate was 12% (6 of 51 patients). There were 3 CSF leaks that required repair/exploration and 2 intracranial infections. One patient developed a delayed subdural hematoma that required an evacuation procedure. One patient had immediate subjective visual worsening and underwent revision of a gasket seal closure because compression of the optic pathway was suspected. The patient's vision improved with an elevation in blood pressure. There were no significant differences between the study groups.

TABLE 1. Distribution of cases for each mutation group based on tumor consistency

Tumor Consistency	*BRAF*	*CTNNB1*	ND
Cystic	5	19	6
Mixed	3	9	1
Solid	3	5	0

Recurrence and Further Treatment

Twelve patients experienced recurrence (24%). Eight of these 12 patients (67%) had not undergone GTR. Of the 36 patients in whom GTR was achieved, tumor regrowth occurred only in 4 patients (11%). Six patients underwent reoperation for recurrence, and 6 patients underwent radiotherapy. Time to recurrence ranged from 1 month to 6 years. The *BRAF* group had the highest rate of GTR and lowest rate of overall recurrence, but this did not reach statistical significance.

Discussion

Optimal treatment of craniopharyngiomas has been controversial. Aggressive resection has the potential of cure; however, it may be associated with significant morbidity rates.[8,12,13] In recent years, there has been an increasing tendency toward subtotal resection of complex craniopharyngiomas followed by adjuvant radiotherapy to maximize quality of life while achieving tumor control.[11,14,22] The rationale for this approach is based on the observation that the life expectancy of patients with craniopharyngiomas is longer than that for patients with other intracranial malignancies,[27,34] and, therefore, treatment should focus on preservation of function and quality of life. The lack of effective chemotherapy further complicates the management of these patients, and the limited understanding of the molecular profile of craniopharyngiomas has challenged the development of new therapies. Recent findings have shown that most ACPs carry a *CTNNB1* mutation (75%–96%)[6,31] and most PCPs carry a *BRAF* mutation (95%).[4] This also underlies the observation that most, but not all, craniopharyngiomas can be categorized as either carrying a *CTNNB1* or a *BRAF* mutation.

The major finding in this study is that the genomic signatures of craniopharyngiomas play a critical role in determining their characteristics. The 3 groups of mutation profiles (*BRAF*, *CTNNB1*, and ND) revealed statistically significant differences in age groups (adult vs pediatric) location (sellar vs nonsellar), and histology (adamantinomatous vs papillary).

TABLE 2. Distribution of cases for each mutation group based on their postoperative hypopituitarism and DI status

Variable	*BRAF*	*CTNNB1*	ND
Hypopituitarism			
Absent	1	8	1
Present	10	25	6
DI			
Absent	2	10	0
Present	9	23	7

Histology

There are 2 histological subtypes of craniopharyngiomas: adamantinomatous and papillary. ACPs were found to contain mutations in the *CTNNB1* gene with variable frequency (75%–96%).[6,31] It was recently reported that PCPs contain *BRAF* (*V600E*) mutations in 95% of cases[4] and that *CTNNB1* and *BRAF* mutations are mutually exclusive and specific to tumor subtype. On the other hand, another study revealed that *BRAF* and *CTNNB1* mutations may coexist in ACP tumors.[18] These findings have a major impact on understanding the molecular mechanisms and new treatment potentials for craniopharyngiomas.

In this study, we found that the *BRAF* group had the papillary subtype exclusively and the *CTNNB1* group had the adamantinomatous subtype. These results are similar to those in previous publications.[1,17,31] Interestingly, the craniopharyngiomas in the ND group were all of the ACP histological subtype. The craniopharyngiomas in the ND group may represent a failure due to technical error, inadequate sampling quantity, and/or inflamed tissue, thus making it difficult to detect a likely *CTNNB1* mutation, considering that they were all ACPs. There is also a possibility that these craniopharyngiomas may contain another currently unknown mutation that creates the ACP phenotype. Marucci et al. found that 3 of 15 (20%) ACP lesions in their study did not carry either the *CTNNB1* or the *BRAF* mutation.[25] Additionally, Scagliotti et al., when they examined an ACP that had been diagnosed in utero, could not find either of the common mutations, concluding that this may represent a subcohort of congenital ACPs.[29] Further genomic analysis of more ACP tumors is required to elicit which additional mutations may be contributing to the propagation of these tumors.[23]

Age Group

When we evaluated the 3 mutation groups based on age groups (pediatric vs adult), we found that there was a statistically significant difference between the groups. There were no pediatric patients in the *BRAF* group, and the ND group had a higher percentage of pediatric patients (43%) than the *CTNNB1* group (15%). It is known that ACPs present in bimodal distribution and that these lesions represent the most common suprasellar lesions in the pediatric population.[5] Our cohort confirmed this; all pediatric patients had histologically proven ACPs and were in either the ND group or the *CTNNB1* mutation group.

Preoperative Vision and Pituitary Function

Regardless of mutation types or histology, craniopharyngiomas located close to visual pathways, the pituitary-hypothalamic system, and the ventricular system cause a combination of neurological and endocrinological symptoms and signs at presentation. In our study, we evaluated preoperative vision, adenohypophysis function (normal vs at least 1 affected hormone [hypopituitarism]), and neurohypophysis function (normal vs DI). These findings are similar to those in other series.[10,15,16,33]

Tumor Size and Radiographic Characteristics

In our series, we found that the majority of craniopharyngiomas were purely extrasellar (61%) and the majority of them were cystic in consistency (59%). This finding is similar to that of previous studies.[33] The craniopharyngiomas in the *BRAF* group were found to be predominantly nonsellar (91%) and noncystic (solid or mixed; 55%). Those in the ND group were predominantly sellar (86%) and nonsolid (cystic or mixed; 100%). The genetic groups correlated significantly with location (sellar vs nonsellar). This finding may represent a link between the driver mutations in craniopharyngiomas and the site of origin and embryological signaling, which was observed in other benign brain tumors of the skull base.[7] The embryology of the sellar area is a complex phenomenon because of the intersection of different tissue types. Anterior diencephalon and the neural crest ectoderm of the pharyngeal vault induce formation of Rathke's pouch, the infundibulum, and early adeno- and neurohypophyses.[26] Further understanding of the different signals and pathways involved in this region will shed additional light on understanding the molecular mechanisms of craniopharyngiomas.

Conclusions

In addition to known genetic mutations (*BRAF* and *CTNNB1*), which are known to correlate with PCP and ACP histological types, respectively, our study revealed a third group that stands separately with respect to patient age and tumor location. These tumors with no known mutations are exclusively of ACP histology, and we found that, compared with the other subtypes, a greater percentage of children harbor these tumors. This group may represent a different, currently unknown mutation, which also leads to the ACP phenotype through a separate pathway.

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Disclosures

Dr. Souweidane reports that he is a consultant for Aesculap.

Author Contributions

Conception and design: Schwartz, Omay. Acquisition of data: Omay, Chen, Almeida, Ruiz-Treviño, Boockvar, Stieg, Greenfield, Souweidane, Kacker, Pisapia, Anand. Analysis and interpretation of data: Schwartz, Omay, Chen, Pisapia. Drafting the article: Omay, Chen, Almeida. Critically revising the article: Schwartz, Omay, Pisapia. Reviewed submitted version of manuscript: Schwartz, Omay. Approved the final version of the manuscript on behalf of all authors: Schwartz. Statistical analysis: Omay. Administrative/technical/material support: Schwartz. Study supervision: Schwartz.

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