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Original Article

Operative considerations for resection of pituitary adenoma in patients with sickle cell disease: A retrospective analysis of 19,653 patients

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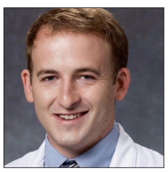

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ABSTRACT

Background: Sickle cell disease (SCD) is a hemoglobinopathy that affects over 30 million individuals worldwide. When significant "sickling" occurs, blood flow to specific organs can be impaired, resulting in ischemia or infarction. This can be problematic during intracranial surgery, in which low systemic circulatory volume due to significant blood loss can lead to intracranial hypotension. Using a multivariable modeling approach, we gathered a large patient dataset through a nationally representative database to inform future neurosurgical management of patients with concurrent SCD and pituitary adenoma.

Methods: We queried the Healthcare Cost and Utilization Project Nationwide Readmissions Database and implemented discharge weighting to identify a cohort of SCD patients who had undergone surgical resection of pituitary adenoma between 2015 and 2016. Variables investigated included patient age, sex, length of stay, postoperative complications and outcomes, payment methods, and median income, among several others.

Results: Retrospective analysis identified 19,612 non-sickle cell patients (NSCP) and 41 SCD patients. Complication profiles for the SCD cohort demonstrated significantly higher rates of postoperative pulmonary embolism ($P = 0.042$) and pneumonia ($P = 0.005$) compared to those of the NSCP cohort. In addition, the SCD cohort trended toward higher rates of readmission (15.25% vs. 9.76%) and deep vein thrombosis, although neither achieved statistical significance ($P = 0.45$ and 0.07, respectively).

Conclusion: SCD is a severe disorder that affects many individuals worldwide and represents a significant risk factor for complications and adverse outcomes in pituitary adenoma surgery. Further research is needed to explore SCD as a risk factor in pituitary surgery and the role it may play in perioperative complications.

Keywords: Apoplexy, Empty sella, Neurosurgery, Pituitary adenoma, Sickle cell disease, Skull base surgery

INTRODUCTION

Sickle cell disease (SCD) is a hemoglobinopathy affecting over 30 million individuals worldwide.[1,7] This disorder is the result of a point mutation in the beta-globin gene that interferes with the normal structure of hemoglobin (and thus the normal oxygen-carrying function of red blood cells [RBCs]).[1] In patients with SCD, pathological hemoglobin S predominates and polymerizes, creating morphologically distorted and rigid "crescent-shaped" RBCs that can occlude blood vessels.[30,33,38] As a result of their increased risk for vaso-occlusive crises, patients with SCD who undergo surgery are prone to developing perioperative complications. SCD predisposes them to an increased risk of acute chest syndrome, congestive heart failure, infection, cerebrovascular accident, and acute kidney injury in the perioperative setting.[1] These severe complications can lead to increased morbidity and mortality for patients with SCD who undergo surgery.[1]

Because surgical procedures appear to increase the risk of pathophysiological complications resulting from SCD, it is important to consider the management of SCD in complex intracranial procedures (such as resection of pituitary adenoma).

At present, a paucity of literature exists informing this topic; as such, there are no guidelines for the minimization of risks in pituitary adenoma patients undergoing transnasal resection of their pituitary lesion. Therefore, in the present study, we explore SCD as a potential perioperative risk factor for complications in the context of surgical management of pituitary adenomas. Using a multivariable modeling approach, we analyze a large patient dataset abstracted from a nationally representative database to inform future neurosurgical management of patients with concurrent SCD and pituitary adenoma.

MATERIALS AND METHODS

Data source

The authors searched the Healthcare Cost and Utilization Project Nationwide Readmissions Database (NRD) to identify a cohort of patients who had undergone surgical resection of pituitary adenoma through endoscopic or microscopic intervention surgery between 2015 and 2016. This dataset featured patients both with and without SCD (any patients with sickle cell trait would have been included in the NSC cohort by default). In addition, to assess various comorbid patient conditions, the International Classification of Diseases, Tenth Revision, and Clinical Modification codes were utilized.

The NRD serves as a nationally representative database ranging from approximately 17 million hospital discharges. It covers data from 22 geographically dispersed states and includes both payers and the uninsured in its data collection. Patient information from rehabilitation and long-term acute hospitals is excluded from the data collection.

Patient sample

From the NRD dataset, discharge weighting was implemented to identify 19,612 non-sickle cell patients (NSCP) and 41 sickle-cell patients (SCP). Patient age, sex, length of stay, postoperative complications and outcomes, payment methods, and median income, among several others, were variables extracted from the NRD. Median income was assessed in quartiles, with quartile I being the top earners and quartile IV comprising those individuals with the lowest incomes. Specific postoperative complications that were compared and contrasted in each patient cohort included perioperative cerebrospinal fluid (CSF) leak, pulmonary embolism, deep vein thrombosis (DVT), hyperosmolarity/hyponatremia, postoperative CSF leak, infection, pneumonia, post hemorrhagic anemia, and acute kidney failure. Hospital readmission was defined as the number of patients who were readmitted postoperatively for any reason within the duration specified.

Statistical analysis

All statistical analyses performed throughout the study were conducted using R Studio (Version 1.4 1106). For analyses, statistical significance was defined as $P < 0.05$. Student's *t*-tests were performed to compare two mean values between cohorts. A binomial-fitted multivariable analysis was performed using the *glm* function in RStudio Version 1.3.1073 (R Foundation for Statistical Computing, Vienna, Austria) to discover associations among variables and

Table 1: Patient demographics.

	Non-sickle cell patients (*n*=19,612)	Sickle cell patients (*n*=41)
Age in years (SD)	52.9±16.9	44.99±13.9
Sex, *n* (%)		
Female	9895 (51)	28 (68)
Male	9717 (50)	13 (32)
Insurance, *n* (%)		
Medicare	5621 (29)	10 (24)
Medicaid	2459 (13)	10 (24)
Private	10265 (52)	19 (46)
Other (Self-Pay/No Charge)	1267 (6)	2 (4.9)
Median income by zip code, *n* (%)		
Quartile 1	4739 (24)	20 (49)
Quartile 2	4886 (25)	8 (20)
Quartile 3	4907 (25)	6 (15)
Quartile 4	4780 (24)	6 (15)
Other	300 (1.5)	1 (2.4)
Hospital type, *n* (%)		
Metropolitan non-teaching	928 (4.7)	0 (0.0)
Metropolitan teaching	18533 (95)	41 (100)
Non-metropolitan	151 (0.8)	0 (0.0)

Table 2: Management and complications in non-sickle cell and sickle cell patients.

	Non-sickle cell patients (*n*=19,612)	Sickle cell patients (*n*=41)	Odds ratio	95% Confidence interval	*P*-value
Mean all-payer cost	25546.08±25366.75	22617.59±18218.46	N/A	N/A	0.46
Mean LOS in days	4.9±7.3	4.7±4.4	N/A	N/A	0.86
CSF leak	3098	9	1.06	0.91–1.24	0.46
Pulmonary embolism	89	1	1.04	1.01–1.07	0.005*
DVT	187	2	1.04	0.997–1.08	0.07
Hyperosmolarity/hyponatremia	1273	2	0.99	0.90–1.1	0.89
Postoperative CSF leak	167	0	0.99	0.96–1.03	0.72
Infection	156	0	0.99	0.955–1.03	0.69
Pneumonia	157	1	1.04	1.0013–1.0797	0.042*
Post hemorrhagic anemia	566	0	0.98	0.91–1.04	0.48
Acute kidney failure	479	2	1.03	0.97–1.1	0.31
Readmission	2990	4	0.94	0.81–1.1	0.45

*Indicates value reaching the level of statistical significance, defined as $P<0.05$. LOS: Length of stay, CSF: Cerebrospinal fluid, DVT: Deep vein thrombosis, N/A: Not applicable

postoperative outcomes. Covariates within the model were grouped respectively as number of patients in each cohort, postoperative complications, and cause of readmission. *Post hoc* odds ratios, 95% confidence intervals, and *P*-values were calculated.

RESULTS

Patient characteristics

In the NSC cohort, the mean patient age at the time of surgery was 52.9 years (standard deviation [SD]: 16.9 years), as compared to 44.99 years (SD: 13.9 years) in the SCD cohort [Table 1]. Sex was relatively well-balanced in both cohorts, with females representing 50.5% and 68.3% of the NSC and SCD cohorts, respectively. When considering median income by zip code, NSC was predominantly in Quartile III (25%), while nearly half of all SCD patients were members of Quartile I (48.8%). For both NSC and SCD patients, the most common insurance type carried was private insurance (52.3% and 46.3%, respectively). In addition, the primary hospital type for NSC and SCD was "Metropolitan Teaching Hospital" (94.5% and 100%, respectively).

Complications for SCP versus NSCP

In the NSC cohort, the mean all-payer cost was $25,546.08 (SD: $25,366.75), with a mean length of stay (LOS) of 4.9 days (SD: 7.3 days) [Table 2]. In the SCD cohort, the mean all-payer cost was $22,617.59 (SD: $18,218.46), while the mean LOS was 4.7 days (SD: 4.4 days). No statistically significant differences between the two cohorts were observed in all-payer costs (P = 0.46) or LOS (P = 0.86). The SCD cohort had significantly higher rates of pulmonary embolism when compared to the NSC cohort (2.4% vs. 0.8%; odds ratio [OR] = 1.040 [95% confidence interval; CI = 1.001–1.078], P = 0.042). In addition, the occurrence of DVTs in patients with SCD approached statistical significance (P = 0.07).

A similar trend was seen in rates of pneumonia, with the SCD cohort having statistically significantly higher rates than the NSC (2.44% vs. 0.45%; OR = 1.04 [95% CI = 1.01–1.07], P = 0.005). Overall, the rates of readmission in the NSC and SCD cohorts are roughly comparable: 15.3% and 9.76% (P = 0.45).

DISCUSSION

SCD increases the risk of perioperative complications in patients undergoing both elective and emergent surgery.[3,16,19,20,23,25-27,35] Recent investigations on the incidence of pituitary adenomas from national registry data suggest that they are more frequent than once thought, with an estimated incidence of 4.8 cases/100,000 persons and a mean age of diagnosis of approximately 50 years old.[11] In the developed world, the average life expectancy for a SCD patient is estimated to lie between 40 and 60 years, with nearly 50% of patients living past the age of 50.[31] This data underscores the relevance of reducing the risk of complications in patients with SCD undergoing resection of pituitary adenomas. Importantly, preoperative planning should consider the patient's baseline hematologic profile, history of transfusion requirements, comorbidities, and opioid use.[1] In the intraoperative setting, care must be taken to avoid hypoxia, acidosis, hypothermia, and volume depletion.[1] Any past medical history of acute sickle cell crises must be carefully considered to avoid potential triggers. In the literature, each of these previously mentioned risks has been evaluated in the context of managing the most common surgical cases in

SCD patients, including cholecystectomy,[11] splenectomy,[31] coronary artery bypass graft,[24] and thrombectomy.[12]

Given the relative prevalence and potential for clinical overlap between pituitary adenoma and SCD, we investigated the influence of SCD on postoperative outcomes in patients undergoing surgical resection of pituitary adenomas. To the authors' knowledge, no retrospective or prospective study has analyzed risks associated with SCD in pituitary adenoma surgery.

Hematological disorders (HDs)

HDs, which encompass conditions that affect primarily blood or blood-producing organs, are known to play a pathological role in various neurological emergencies and conditions.[2,13] HDs account for 1.3% of all acute stroke cases and are of particular concern in patients with prior venous thrombosis.[2] Interestingly, the association between SCD and DVT in pituitary adenoma resection approached statistical significance ($P = 0.07$) in this study and is worthy of further investigation. When specifically examining the role of HD in pituitary adenoma surgery, it is thought that anemia may increase the risk of pituitary apoplexy.[10] Given that pituitary surgery is associated with the potential risk of extensive bleeding, potentially requiring blood transfusion, anemic patients might be at increased risk for apoplexy.[32] One propensity-matched analysis found that patients undergoing sinus surgery who presented preoperatively with anemia were at a higher risk of bleeding and postoperative complications, including ventilator support for greater than 48 hours and acute renal failure.[18,32] Clearly, if anemia can predispose patients to cardio and cerebrovascular events during surgery, it is logical that SCD associated hypoxia could represent a precipitant of apoplexy, stroke, and/or other complications during surgical resection of pituitary adenomas.

Pituitary apoplexy

Pituitary apoplexy, which can result from hemorrhage into the pituitary gland or occlusion of glandular blood flow, is an extremely dangerous complication noted in anemic patients undergoing pituitary surgery.[6,9,15,26] More specifically, anemic patients undergoing surgery have a higher risk of bleeding, which, when related to pituitary apoplexy, can lead to bleeding within a tumor in the pituitary region or apoplexy in postoperative residual disease.[32,36] Therefore, current guidance, as outlined in the literature, is to treat the patients' anemia before pituitary surgery to minimize the risk of potential apoplexy.[6]

Cerebrovascular conditions

This is important because SCD has been found to have a particularly large impact on cerebrovascular conditions.[5,33] Patients with SCD are reportedly at risk for the formation of spontaneous epidural hematomas, a potential intraoperative complication in this population.[4,14] One possible explanation for this phenomenon is that infarction of the skull base leads to periosteal elevation, disruption of the cortical bone margin, and, ultimately, bleeding into the epidural space.[14,34] This was an outcome that the authors were unable to measure in the present study. Of note, the presence of epidural hematomas is primarily associated with bone infarctions rather than transsphenoidal surgery itself.

In addition, ischemic stroke is a potentially major neurological complication of SCD.[17,29,37] Given that pituitary tumors can cause tremendous mass effect on the optic chiasm, the predilection for occlusive events in SCD patients, particularly in the microvasculature supplying the optic chiasm, can lead to significant postoperative visual morbidity after pituitary surgery.

Pulmonary embolism

Through multivariable analysis, the authors identified that, for patients with SCD who underwent pituitary adenoma resection, pulmonary embolism ($P = 0.005$) and pneumonia ($P = 0.042$) were each significant postoperative complication. While the mechanism by which SCD affects various complications is yet unknown, it is established that patients with SCD are in a hypercoagulable state at baseline. This hypercoagulability causes blood flow augmentation and turbulence that may promote endothelial cell damage, predisposing to thrombus formation.[39] In their cohort of 245 adults with SCD who were imaged for suspected pulmonary embolism, Tivnan *et al.* found that 27 (11%) were diagnosed with a pulmonary embolism at least once in their 17-year study period.[39] In the present study, the SCD cohort had significantly higher rates of pulmonary embolism than the NSC cohort (2.4% vs. 0.8%, respectively; OR = 1.040 [95% CI = 1.001–1.078], $P = 0.042$). Importantly, while this particular OR is small, this finding could potentially be constrained by the small sample size of the SCP cohort ($n = 41$), which contributes to limited statistical power.

Pneumonia

Pneumonia, a potentially serious infection, was also identified in the present study as a significant postoperative complication for patients with SCD who had undergone resection of a pituitary adenoma. Infection contributes significantly to morbidity and mortality in SCD as the sickle cell gene leads to an increased risk of infection for these patients as a result of functional asplenia.[8] For example, functional asplenia resulting from long-term SCD may increase the rates of pneumonia in the SCD.[21] Specifically, nosocomial encapsulated organisms, such as *Streptococcus pneumoniae*, may largely affect functionally asplenic SCD patients, resulting in higher rates of pneumonia.[28] Finally, as Liu *et al*.[22] highlight in their report some patients who undergo pituitary adenoma surgery and undergo reconstruction with foreign material, such as hydroxyapatite cement or titanium mesh plates, may be at increased risk for representation with seller inflammation and purulence, as well as bacterial infections.[22] Therefore, SCD is potentially at risk of infection due to the functional status of their immune system, particularly when such foreign material is used in pituitary surgery. Although we observed the rate of infection to be only slightly higher in SCD, the small sample size of the SCD cohort may have prevented our study from reaching the statistical power necessary to detect a larger difference.

Importantly, the present study was the first multivariable analysis to evaluate the impact of SCD in pituitary surgery. Although previous studies have described the impact of SCD on various neurological diseases, this body of literature is relatively limited. Therefore, by providing a multivariable analysis specific to SCD patients undergoing pituitary surgery, the authors underscore the importance of specialized care for SCD patients when conducting pituitary adenoma resection and add to the overall literature informing care of patients with SCD.

Limitations

We acknowledge several limitations to the present study. First, the fact that the database only includes data from patients readmitted to the hospital means that it is, by definition, not reflective of the general population of all patients with SCD undergoing pituitary surgery. This introduces the potential for Bergson's bias to affect the results we obtained. Future studies should leverage data from several registries to mitigate bias and maximize generalizability. Furthermore, due to the limited granularity of the database, comorbid patient conditions were unable to be identified for each patient. As a result, these potentially relevant variables were unable to be accounted for. Along these lines, complications commonly associated with SCD, such as stroke, spontaneous hematoma, take-back surgery for postoperative hematoma, and vision loss/complications, were not identifiable outcomes. Further, given our study analyzed patients from 2014-2015, this serves as a potential limitation regarding data collection. Finally, a key limitation of the present study is the small sample size of the SCD cohort, particularly when compared to the NSC cohort.

CONCLUSION

SCD represents a severe disorder that affects over 30 million individuals worldwide. Previous literature has failed to describe SCD as a risk factor in the context of pituitary adenoma surgery. To optimize neurosurgical care and patient outcomes, additional research is needed to explore further these complications and the mechanisms by which they arise in patients with SCD undergoing resection of pituitary adenoma.

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