Comparative analysis of pituitary adenoma with and without apoplexy in pediatric and adolescent patients: a clinical series of 80 patients

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Abstract

Object

Pituitary adenomas (PAs) have a low incidence in pediatric and adolescent patients, and their clinical characteristics remain unclear. As a severe complication of PA, apoplexy was investigated in young patients in the present study.

Methods

Eighty consecutive patients younger than 20 years with PAs who underwent surgery were included. The study cases were divided into an apoplexy group and non-apoplexy group, and the corresponding clinical data were statistically analyzed and compared between these two groups.

Results

The study included 33 males and 47 females, with a mean age of 16.9 years. There were six (7.5%) ACTH-secreting, 13 (16.3%) GH-secreting, 47 (58.7%) PRL-secreting, and 14 (17.5%) non-functioning PAs. There were 34 (42.5%) patients in the apoplexy group and 46 (57.5%) patients in the non-apoplexy group. Preoperatively, patients in the apoplexy group were more likely to have visual impairment (P = 0.033, HR = 2.841, 95% CI = 1.073–7.519) and had poorer visual impairment scores than those in the non-apoplexy group (P = 0.027). Although not statistically significant, apoplexy may have been associated with a higher Ki-67 proliferation index (P = 0.070). However, apoplexy was not associated with tumor type, tumor size, resection rate, or tumor recurrence.

Conclusion

Tumor apoplexy was common in pediatric and adolescent patients with PAs, and was associated with more severe preoperative visual deficits. Hence, appropriate surgical treatment may be important for salvaging visual function in young PA patients.

Introduction

Although pituitary adenoma (PA) is the third most common intracranial tumor in adults, its incidence in pediatric and adolescent patients (under the age of 20 years) is low, accounting for approximately 2.6–6.1% of all pituitary tumor [5, 16] and 1% of all intracranial tumors [30] in pediatric and adolescent patients. Nevertheless, previous studies [7, 16] have shown that young patients with PAs may have unique clinical and pathological characteristics that require distinct analyses and considerations.
Apoplexy is a major complication of pituitary tumors and may result in sudden headaches, visual deficits, vomiting, and other symptoms [13]. However, the specific clinical features of pituitary adenoma apoplexy (PAA) remain unclear in pediatric and adolescent patients due to the small number of reported cases. Moreover, conflicting results have been found in the literature concerning the clinical and prognostic implications of PAA in young patients [15, 33].

In the present study, we analyzed clinical data from 80 pediatric and adolescent patients with PAs. We divided these patients into an apoplexy group and non-apoplexy group and compared their clinical characteristics.

**Materials And Methods**

**Patients**

Between January 2011 and February 2019, 3,137 consecutive patients were diagnosed with PA and underwent surgery in the Department of Neurosurgery at The First Hospital of China Medical University. There were 80 (2.6%) patients under the age of 20 years who were included in the present study. All patients underwent transsphenoidal surgery. This study was approved by the institutional review board at The First Hospital of China Medical University, and written informed consent was obtained from each patient and their parent(s) for the use of clinical data for future research.

**Clinical examinations**

All patients routinely underwent pre- and post-operative hormonal tests, magnetic resonance imaging (MRI) of the sellar region, and visual examinations. The degree of tumor invasion to the supra- and parasellar regions was graded by the Hardy-Wilson classification and Knosp classification, respectively. Tumor apoplexy was determined through preoperative MRI (Fig. 1) and intraoperative observation. Visual acuity and visual fields were evaluated, and the visual impairment score (VIS) of the German Ophthalmological Society was recorded, as previously described [8]. Tumor size was calculated using the ellipsoid volume formula: \( V = \pi abc/6 \), in which a, b, and c denote the anteroposterior diameter, transverse diameter and axial diameter, respectively. Resection rate was determined by comparison of pre- and post-operative MRI scans. Near total resection (NTR) was defined as more than 90% tumor resection, while subtotal resection (STR) was defined as less than 90% tumor resection.

Abnormal hormonal levels were assessed based on baseline hormonal levels, as follows: luteinizing hormone (LH), 6–34 mIU/mL; follicle-stimulating hormone (FSH), 2–22 mIU/mL; prolactin (PRL), 1.5–30 μg/L; growth hormone (GH), 0.05–10 μg/L; insulin-like growth factor-I (IGF-1), 10–500 ng/mL; adrenocorticotropic hormone (ACTH), 30–60 pg/mL; and cortisol (COR), 171–536 nmol/L forenoon and 64–327 nmol/L afternoon. Tumor classification was determined by preoperative hormonal assays, clinical symptoms, and postoperative pathology and immunohistochemistry (provided by the Department of Pathology at The First Hospital of China Medical University). The mean follow-up time was 67.6 ± 26.8 months (range 23–111 months).
Statistical analysis

Logistic regression, χ² tests, and t-tests were used to evaluate risk factors of apoplexy and for comparisons between the two groups. All statistical analyses were performed using SPSS v25.0 (SPSS Inc., Chicago, IL). P<0.05 was defined as statistically significant.

Results

Clinical features

As shown in Table 1 and Table 2, a total of 33 (41.3%) males and 47 (58.7%) females between the ages of 10 and 20 years (mean age 16.9 ± 2.2 years) were included in the present analysis. There were six (7.5%) ACTH-secreting, 13 (16.3%) GH-secreting, 47 (58.7%) PRL-secreting, and 14 (17.5%) non-functioning PAs. The average tumor size was 9.0 cm³. The Hardy-Wilson classification was used to evaluate suprasellar invasion in each patient, among whom 24 (30.0%) patients were Grade A, 17 (21.3%) patients were Grade B, 12 (15.0%) patients were Grade C, 12 (15.0%) patients were Grade D, and 15 (18.7%) patients were Grade E. The Knosp classification was used to assess para-sellar invasion in each patient, among whom 26 (32.5%) patients were Grade 0, 24 (30.0%) patients were Grade 1, 7 (8.8%) patients were Grade 2, 10 (12.5%) patients were Grade 3, and 13 (16.2%) patients were Grade 4. All patients underwent transsphenoidal surgery, among whom 35 (43.8%) patients received endoscopic surgery and 45 (56.2%) patients received microscopic surgery. Sixty-six (82.5%) patients received NTR. During the follow-up period, 10 (12.5%) patients were confirmed to exhibit tumor recurrence. The median progression-free survival (PFS) was 24 months (ranging from 3–69 months), and the average age at the time of tumor recurrence was 20.1 ± 2.4 years. Eleven patients (13.8%) with PRL-secreting tumors received long-term bromocriptine treatment after surgery. Twenty patients (25.0%) with hypopituitarism received long-term hormone replacement therapy. In the 10 patients with tumor recurrence, five were treated with secondary surgery, three with PRL-secreting tumors were treated with bromocriptine, and the remaining two patients were followed up closely due to their asymptomatic recurrence.

Comparison of tumors with and without apoplexy

The apoplexy group included 34 (42.5%) patients while the non-apoplexy group included 46 (57.5%) patients. The patients’ sex, age, preoperative body mass index (BMI), visual function, tumor types, hypopituitarism, tumor size, supra- and para-sellar invasion, surgical approach, extent of resection, and duration of surgery were compared between the two groups. Results are presented in Table 1 and Table 2. There were 15 and 10 patients who suffered visual deficits during the pre-operative period among the apoplexy group and non-apoplexy group, respectively. More patients in the apoplexy group showed preoperative visual abnormalities (P=0.033, HR=2.841, 95% CI=1.073–7.519; Fig. 2a). Patients in the apoplexy group had significantly worse preoperative VIS than those in the non-apoplexy group (P=0.027; Fig. 2b). Although surgery improved visual function in both groups, the postoperative VIS of the apoplexy group was still worse than that of the non-apoplexy group (P=0.034; Table 1). PAA was not associated
with sex (P=0.364), age (P=0.383), or preoperative hypopituitarism (P=0.655). Postoperatively, six patients (17.6%) in the apoplexy group and 14 patients (30.4%) in the non-apoplexy group with hypopituitarism received long-term hormone replacement therapy (P=0.192). There were also no significant differences between the two groups in terms of tumor size (P=0.848) or invasiveness (Hardy-Wilson classification, P=0.142; Knosp classification, P=0.117). PAA also did not significantly affect operative time (P=0.192) or resection rate (P=0.572). Although not statistically significant, PAA may have been associated with a higher Ki-67 proliferation index (P=0.070; Fig. 2c).

As shown in Table 3, tumor apoplexy was not associated with postoperative tumor recurrence (P=0.608, HR=1.414, 95% CI=0.375–5.319; Fig. 2d). Cox multivariate regression analysis demonstrated that only STR was independently related to postoperative tumor recurrence (P=0.019, HR=4.556, 95% CI=1.276–16.260), although Knosp classification (P=0.043, HR=3.533, 95% CI=1.004–12.563; Fig. 2e) and STR (P=0.045, HR=4.000, 95% CI 0.956–16.667; Fig. 2f) were both significantly associated with recurrence in univariate regression.

**Discussion**

PAA was first reported in 1898 and first summarized in cases in 1950 [1]. As a severe complication, in adult PA patients, the overall incidence of apoplexy is 0.6–25% [13, 17, 23, 25], and it is more likely to occur in those aged 30–50 years [32]. Hypotheses concerning the pathogenesis of PAA include the following: hypertension [13, 21] or acute hypotension [20, 26]; history of pelvic, cardiac, or vascular surgery [11, 13, 31]; history of anti-platelet and/or anticoagulant medication [11, 13, 17, 18, 26]; history of gonadotropin-releasing hormone medication [21] or dopamine-agonist medication; trauma [21]; presence of aneurysms [22]; and radiotherapy [21, 31]. However, none of the pediatric and adolescent patients in the present study had any of the above histories or clinical features. Large tumor size [18], imbalance of high local metabolism, and low nutritional status [20] may also lead to local vascular occlusion and rupturing, and may result in the development of apoplexy. Moreover, molecular factors (e.g., vascular endothelial growth factor [12], high-mobility group box 1 [19], oestrogen [14], and AIP mutation [27]) may also contribute to the development of apoplexy by altering microvascular permeability, promoting local subacute intra-tumoral inflammatory responses, and inducing faster growth of tumor cells. However, PAA has not been thoroughly described in pediatric and adolescent patients due to limited published cases.

In the present study, apoplexy was found in 42.5% of pediatric and adolescent PAs. This result is consistent with previous reports that the prevalence of PAA in pediatric and adolescent patients is higher than that in adult patients (approximately 0.6–25%) [13, 17, 23, 25]. Moreover, consistent with previous reports, although apoplexy is more frequently found in non-functional tumors in adults [33], the present study corroborated that more PAs with apoplexy are functional tumors in pediatric and adolescent patients [6, 16]. Although the precise reason for this phenomenon remains unclear, there are some plausible speculations. In adult patients, functional PAs are often detected by specific hormone-secreting symptoms, while non-functional PAs are often detected by apoplexy causing a sudden increase in tumor
size and an obvious occupying effect. In contrast, the majority of PAs in pediatric and adolescent patients are functional [3, 9, 10], and non-functioning PA is extremely rare in young patients [28]. Moreover, hormonal symptoms cannot be easily identified in the growing stages of each organ; therefore, apoplexy-related symptoms are frequently found in functional PAs in younger patients.

Some authors have reported that in pediatric and adolescent patients, PAA may be associated with tumor size, tumor invasiveness, and PRL-secretory type [33]. However, others studies have not found such associations [15]. Similarly, in our present study, apoplexy did not relate to tumor size, Knosp/Hardy-Wilson classifications, or PRL tumors. Nevertheless, our results indicate that, as in adult patients [13], PAA is significantly associated with preoperative visual loss and/or deficits in pediatric and adolescent patients. Although surgery improved visual function in both groups, the postoperative VIS of the apoplexy group was still worse than that of the non-apoplexy group. In these cases, early surgery to decompress the optic nerves is critical. It has been reported that it is optimal to operate within one week or even 48 h, which can reduce the rate of disability [2, 24]. Therefore, appropriate surgical management is essential for pediatric and adolescent patients with PAA to salvage visual function. Moreover, our present findings suggest that young PA patients with apoplexy might have a higher Ki-67 proliferation index than those without apoplexy (P=0.070), indicating that apoplexy-inducing PAs may have a tendency for rapid growth; if so, this would induce an insufficient blood supply and an ischemic-hypoxic tumor microenvironment, leading to PAA [29].

We also investigated the effect of apoplexy on tumor recurrence in pediatric and adolescent patients. We found that the presence of tumor apoplexy did not affect tumor resection, and was not associated with tumor recurrence. Furthermore, using multivariate analysis, only STR was found to be independently associated with recurrence, and Knosp classification correlated with resection rate.

Limitations

Our study had the following limitations. This was a retrospective study with a limited sample size, and bias may have existed. Thus, more favorable clinical evidence is still needed from subsequent large-sample prospective studies.

Conclusions

Tumor apoplexy is common in pediatric and adolescent patients with PA and is associated with more severe preoperative visual deficits. Therefore, appropriate surgical treatment may be important for salvaging visual function.

Declarations

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Availability of data and material: The data and material required had already been contained in this article.

Code availability: Not applicable.

Ethics approval: This study was approved by the institutional review board at The First Hospital of China Medical University.

Consent to participate: Written informed consent was obtained from each patient and their parent(s) for the use of clinical data for future research.

Consent for publication: Written informed consent was obtained from each patient and their parent(s) for publication.

Authors' contributions: RW, ZW, YS, LL and XH cooperated to complete the study. RW, ZW, LL, XH and SH contributed to the collection and analysis of data. RW, ZW and YS participated in drafting the text and figures. SH designed the study and gave indispensable guidance in drafting the manuscript. All authors have read and approved the final manuscript.

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Tables
| Cases no.                  | With apoplexy (%) | No apoplexy (%) | Total (%) | $P$ value of $t$ test | $P$ value of $\chi^2$ test |
|---------------------------|-------------------|-----------------|-----------|-----------------------|---------------------------|
| Total                     | 34                | 46              | 80        |                       |                           |
| Sex                       |                   |                 |           | 0.364                 |                           |
| Male                      | 16 (47.1%)        | 17 (37.0%)      | 33        |                       |                           |
| Female                    | 18 (52.9%)        | 29 (63.0%)      | 47        |                       |                           |
| Age                       |                   |                 |           | 0.383                 |                           |
| Mean ± SD                 | 16.6 ± 2.6        | 17.2 ± 1.9      | 16.9 ± 2.2|                       |                           |
| Preoperative BMI           |                   |                 |           | 0.148                 |                           |
| Mean ± SD                 | 24.6 ± 5.3        | 22.6 ± 4.2      | 23.4 ± 4.7|                       |                           |
| Preoperative vision        |                   |                 |           | 0.033                 |                           |
| Normal                    | 19 (55.9%)        | 36 (78.3%)      | 55        |                       |                           |
| Abnormal                  | 15 (44.1%)        | 10 (21.7%)      | 25        |                       |                           |
| Preoperative VIS           |                   |                 |           | 0.027                 |                           |
| Mean ± SD                 | 19.6 ± 21.3       | 8.8 ± 17.6      |           |                       |                           |
| Postoperative VIS          |                   |                 |           | 0.034                 |                           |
| Mean ± SD                 | 16.9 ± 21.3       | 7.8 ± 16.1      |           |                       |                           |
| Tumor types               |                   |                 |           | 0.326                 |                           |
| ACTH -secreting           | 2 (5.9%)          | 4 (8.7%)        | 6         |                       |                           |
| GH -secreting             | 4 (11.8%)         | 9 (19.6%)       | 13        |                       |                           |
| PRL -secreting            | 25 (73.5%)        | 22 (47.8%)      | 47        |                       |                           |
| Non-functional            | 3 (8.8%)          | 11 (23.9%)      | 14        |                       |                           |
| Preoperative pituitary function |             |                 |           | 0.655                 |                           |
| No hypopituitarism        | 19 (55.9%)        | 23 (50.0%)      | 42        |                       |                           |
| Hypopituitarism           | 15 (44.1%)        | 23 (50.0%)      | 38        |                       |                           |
| Tumor size                |                   |                 |           | 0.848                 |                           |
| Mean ± SD                 | 5.7 ± 5.1         | 11.3 ± 23.7     | 9.0 ± 18.4|                       |                           |
| Classification          | Number | Percentage | Total |
|-------------------------|--------|------------|-------|
| Hardy-Wilson            |        |            |       |
| Grade A                 | 8      | 23.5%      | 24    |
| Grade B                 | 11     | 32.4%      | 17    |
| Grade C                 | 4      | 11.8%      | 12    |
| Grade D                 | 3      | 8.8%       | 12    |
| Grade E                 | 8      | 23.5%      | 15    |
| Knosp                   |        |            |       |
| Grade 0                 | 8      | 23.5%      | 26    |
| Grade 1                 | 15     | 44.1%      | 24    |
| Grade 2                 | 4      | 11.8%      | 7     |
| Grade 3                 | 3      | 8.8%       | 10    |
| Grade 4                 | 4      | 11.8%      | 13    |
| Ki-67 proliferation index|        |            |       |
| Ki-67 ≥3%               | 21     | 61.8%      | 40    |
| Ki-67 <3%               | 13     | 38.2%      | 40    |

SD = standard variation, BMI = body mass index, ACTH = adrenocorticotropic hormone, GH = growth hormone, PRL = prolactin
| Surgical characteristics | With apoplexy | No apoplexy | P value of t test | P value of χ² test |
|--------------------------|--------------|-------------|------------------|-------------------|
| Total                    | 34           | 46          |                  | 0.608             |
| Surgical approach        |              |             |                  |                   |
| Endoscopic               | 16 (47.1%)   | 19 (41.3%)  | 0.608            |                   |
| Microscopic              | 18 (52.9%)   | 27 (58.7%)  |                  |                   |
| Resection degree         |              |             | 0.572            |                   |
| NTR                      | 29 (85.3%)   | 37 (76.1%)  |                  |                   |
| STR                      | 5 (14.7%)    | 9 (23.9%)   |                  |                   |
| Duration of surgery      |              |             | 0.192            |                   |
| Mean ± SD                | 92.1 ± 45.3  | 126.0 ± 108.4 |                  |                   |
| Tumor recurrence         |              |             | 0.608            |                   |
| Yes                      | 5 (14.7%)    | 5 (10.9%)   |                  |                   |
| No                       | 29 (85.3%)   | 41 (89.1%)  |                  |                   |

NTR = Near total resection, STR = subtotal resection, SD = standard variation
### Table 3 The risk factors of recurrence

| Risk factors                              | Cases No. |  |  |  |  |
|-------------------------------------------|-----------|---|---|---|---|
|                                            |           | Recurrence | No recurrence | P value<sup>1</sup> | P value<sup>2</sup> |
| Total                                     |           | 10          | 70            | -                        | -                        |
| Sex                                       |           | 0.304       |               |                           |                           |
| Male                                      |           | 6 (60.0%)   | 27 (38.6%)    |                           |                           |
| Female                                    |           | 4 (40.0%)   | 43 (61.4%)    |                           |                           |
| Age                                       |           | 0.440       |               |                           |                           |
| Mean ± SD                                 |           | 17.1 ± 2.3  | 16.9 ± 2.2    |                           |                           |
| Tumor size                                |           | 0.207       |               |                           |                           |
| Mean ± SD                                 |           | 22.6 ± 4.3  | 23.5 ± 4.7    |                           |                           |
| Hardy-Wilson classification               |           | 0.311       |               |                           |                           |
| Grade A&B                                 |           | 3 (30.0%)   | 37 (52.9%)    |                           |                           |
| Grade C,D,E                               |           | 7 (70.0%)   | 33 (47.1%)    |                           |                           |
| Knosp classification                      |           | 0.043       | 0.249         |                           |                           |
| Grade 0, 1&2                              |           | 4 (40.0%)   | 53 (75.7%)    |                           |                           |
| Grade 3&4                                 |           | 6 (60.0%)   | 17 (24.3%)    |                           |                           |
| Surgical approach                         |           | 0.349       |               |                           |                           |
| Endoscopic                                |           | 3 (30.0%)   | 32 (45.7%)    |                           |                           |
| Microscopic                               |           | 7 (70.0%)   | 38 (54.3%)    |                           |                           |
| Resection degree                          |           | 0.045       | 0.019         |                           |                           |
| NTR                                       |           | 6 (60.0%)   | 60 (85.7%)    |                           |                           |
| STR                                       |           | 4 (40.0%)   | 10 (14.3%)    |                           |                           |
| Apoplexy                                  |           | 0.608       |               |                           |                           |
| Yes                                       |           | 5 (50.0%)   | 29 (41.4%)    |                           |                           |
| No                                        |           | 5 (50.0%)   | 41 (58.6%)    |                           |                           |
| Ki-67                                     |           | 0.176       | 0.287         |                           |                           |
| ≥3%                                       |           | 7 (70.0%)   | 33 (47.1%)    |                           |                           |
| <3%                                       |           | 3 (30.0%)   | 37 (52.9%)    |                           |                           |
1 P value of univariate analysis
2 P value of multivariate analysis