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Original Article

Diagnosis and surgical treatment of adrenal ganglioneuroma: a retrospective cohort study of 51 patients in a single center

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Abstract: Objectives: To analyze the clinical features, imaging findings, and surgical results of 51 cases of adrenal ganglioneuroma (AGN) in our center to provide a clinical reference for its diagnosis and treatment. Methods: We retrospectively reviewed the clinical data of 51 AGN patients admitted to our hospital. We summarized the clinical and imaging characteristics and analyzed the effects of different surgical methods and tumor size on the perioperative outcome. Results: The mean tumor size was 6.1±2.4 cm. The mean computerized tomography (CT) value of tumors on the plain scan images was 29.9±4.3 Hounsfield units (HU), and 60.8% (20/45) of tumors showed delayed progressive enhancement on enhanced CT images. Pathologically, immunohistochemistry revealed a positive rate of 91.7% for S-100 (11/12) and 77.8% (7/9) for Vimentin. Of the 51 patients, 32 underwent laparoscopic adrenalectomy, and 19 underwent open adrenalectomy. The median postoperative follow-up time was 51.1 (2-125) months, and no tumor recurrence or metastasis occurred during the follow-up. The estimated blood loss (EBL) was reduced in the laparoscopic group compared to the open group (P=0.027). Larger tumors prolonged the operation time and postoperative hospital stay (both P<0.05). Conclusions: This study reports the largest series of AGN patients to date. CT plays a guiding role in the preoperative diagnosis of AGN, but the pathologic results are the most reliable. Laparoscopic adrenalectomy may be safer than open surgery. Larger tumor volume is a risk factor for a longer operative time and postoperative hospital stay.

Keywords: Adrenal ganglioneuroma, imaging characteristics, immunohistochemistry, perioperative outcomes

Introduction

Tumors originating from primitive neural crest cells include ganglioneuroma (GN), neuroblastoma and ganglioneuroblastoma, among which neuroblastoma is a highly malignant and poorly differentiated tumor [1, 2]. The nature and biologic behavior of ganglioneuroblastoma fall between those of benign and malignant tumors. GN is a well-differentiated benign tumor and is one of the least aggressive and rarest of all tumors derived from neural crest cells [3]. According to statistics, GN accounts for approximately 0.1% to 0.5% of all nervous system tumors [4]. The most common sites of GN are the retroperitoneum and posterior mediastinum, and the probability of GN occurring in the adrenal gland is approximately 20% to 30% [5, 6].

Although adrenal ganglioneuroma (AGN) generally has the biologic behavior of a benign tumor, when the tumor is large, symptoms of compression can occur and can cause pain or discomfort to the patient [7]. In addition, a few studies have reported recurrence or malignant transformation after GN resection [8]. Based on these characteristics of AGN, surgical resection of the tumor is recommended once the disease is identified. At present, several studies have described the epidemiological characteristics, imaging findings, and treatment of AGN, but the number of cases included is small, and the data are not sufficiently comprehensive [2, 9]. Therefore, to systematically describe and analyze AGN, this study comprehensively reviewed the clinical data of 51 patients with AGN diagnosed in our center during the last decade. In addition, we analyzed the influence of surgical

method and tumor size on perioperative outcome.

Materials and methods

The clinical data were collected from AGN patients admitted to the First Affiliated Hospital of Nanchang University from March 2012 to June 2022. The inclusion criteria were as follows: patients who underwent adrenalectomy in our hospital. The postoperative specimen was pathologically confirmed as AGN. The exclusion criteria were as follows: patients who did not undergo a computerized tomography (CT) scan before the operation, pathological examination of postoperative specimens failed to make a definite diagnosis, or medical records are incomplete. All patients signed an informed consent form. Our study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (2022CDYFYYLK09-044).

Diagnostic work-up

Demographic values, such as sex, age, body mass index (BMI) and clinical presentation, were collected and analyzed. All patients underwent CT scans before the operation. The CT value of the tumor, the presence of calcification and cystic changes, the boundary and shape of the tumor, and the enhancement pattern of the tumor after enhanced scanning were analyzed. Baseline hormone levels were assessed in all patients before surgery. The evaluation content included cortisol, dopamine, norepinephrine, epinephrine, adrenocorticotropic hormone, and serum potassium. The levels of 24 h urinary dopamine, norepinephrine, epinephrine, and vanillylmandelic acid were also evaluated.

Operations

Indications for surgery include pain or discomfort caused by the tumor, tumor diameter greater than 4 cm, suspected malignancy on imaging, short-term tumor enlargement, or elevated hormone levels suggestive of a functional tumor. Laparoscopic adrenalectomy or open adrenalectomy may be selected according to the results of preoperative evaluation or the surgeon's personal preference. In general, laparoscopic adrenalectomy is preferred if the patient cannot tolerate open surgery, if the tumor exhibits signs of benign tumor on imaging, or if the tumor is expected to be easily resectable. Otherwise, open surgery is chosen. In addition, surgeons tended to opt for open surgery in the first few years of this study, whereas laparoscopic adrenalectomy was more preferred in recent years, which is related to advances in laparoscopic technology. The perioperative parameters to be evaluated included operative time, estimated blood loss (EBL), postoperative complications, and postoperative hospital stay.

Histologic evaluation and follow-up

All surgical specimens underwent routine macroscopic and microscopic evaluation of tumor size, weight, texture, and tumor composition. In cases where no definite diagnosis can be made, immunohistochemical examinations, including S-100, vimentin, and neuron-specific enolase (NSE), were performed. The patients were followed up every three months in the first year after surgery. Then, CT examination and hormone level assessments were performed annually [10]. For patients who could not come to our hospital for review, we evaluated the condition by telephone.

Statistical analysis

All data were statistically analyzed using IBM SPSS 26.0. Continuous variables conforming to a normal distribution were expressed as the mean ± standard deviation (SD) and analyzed with a t test. Continuous variables that did not fit a normal distribution were expressed as medians and ranges and analyzed with the Mann-Whitney Wilcoxon test. Counted data were evaluated by the chi-square test. $P<0.05$ was considered significant.

Results

Clinical and hormonal findings

From January 2012 to August 2022, a total of 1856 patients underwent adrenalectomy or adrenal tumor resection in our hospital, and a total of 51 patients were eventually diagnosed with AGN with an incidence rate of approximately 2.74%. There were more male patients than female patients. Thirty-two of the 51 patients (62.8%) did not experience any discomfort, except for the presence of the tumor during the physical examination. The remaining 19 patients (37.2%) reported pain, discomfort, or hypertension. Only 2 of the 51 patients had

Table 1. Clinical data of 51 AGN cases

Characteristic	Value
Age, mean (SD), year	41.2 (17.6)
Gender	
Male, n (%)	30 (58.8)
Female, n (%)	21 (41.2)
BMI	
≥24, n (%)	16 (31.4)
<24, n (%)	35 (68.6)
Elevated hormone levels, n (%)	2 (3.9)
Clinical presentations	
Incidental, n (%)	32 (62.8)
Abdominal/back pain or discomfort, n (%)	13 (25.4)
Hypertension, n (%)	6 (11.8)
Tumor site	
Left, n (%)	24 (47.1)
Right, n (%)	27 (52.9)
Tumor size on pathology, mean (SD), cm	6.1 (2.4)

Note: AGN: Adrenal ganglioneuroma; BMI: Body mass index; SD: Standard deviation.

Table 2. CT findings of 51 AGN patients

Variable	Value
Tumor shape	
Regular, n (%)	29 (56.9)
Irregular, n (%)	22 (43.1)
Tumor border	
Clear, n (%)	47 (92.2)
Unclear, n (%)	4 (7.8)
Calcification, n (%)	8 (15.7)
Cystic degeneration, n (%)	6 (11.8)
Delayed progressive enhancement, n (%)	25/40 (62.5)
Unenhanced CT value, mean (SD), HU	29.9 (4.3)

Note: CT: computerized tomography; AGN: Adrenal ganglioneuroma; SD: Standard deviation; HU: Hounsfield unit.

elevated baseline hormone levels, but no symptoms were noted. The specific demographic and clinical characteristics of the 51 patients are shown in **Table 1**.

Imaging findings

All patients underwent CT examination before the operation. The mean CT value was 29.9±4.3 Hounsfield units (HU). The tumor boundary was clear in 47 of 51 cases (92.2%). Calcification was observed in only 8 cases (15.7%), and cystic degeneration was observed in 6 cases (11.8%). Forty of the 51 patients underwent enhanced CT scans, and 25 (62.5%) of the tumors showed delayed progressive enhancement. The specific imaging features of 51 patients are shown in **Table 2**.

Surgical outcomes and follow-up

Of the 51 patients, 32 (62.8%) underwent laparoscopic adrenalectomy, and 19 (37.2%) underwent open adrenalectomy. The overall incidence of postoperative complications was 17.6%. All complications were mild and improved after treatment. The mean postoperative hospital stay was 5.7±1.3 days. The operation time and EBL were within acceptable limits. The median follow-up time was 51.1 (2-125) months, during which no recurrence or metastasis occurred (**Table 3**).

According to the different surgical methods, we divided the patients into a laparoscopic group and an open group and analyzed the impact of these two surgical methods on the patients. The results showed that patients in the laparoscopic group had smaller tumors, reduced tumor weight, and less EBL (all P<0.05, **Table 4**). We also divided patients into a <6 cm group and a ≥6 cm group according to tumor size and evaluated the perioperative outcomes in both groups. The results showed that larger tumors were associated with longer operative times, greater EBL and longer postoperative hospital stays (all P<0.05, **Table 5**).

Pathology findings

The pathological features of the tumors are shown in **Table 6**. Macroscopically, the tumors were mostly nodular masses with clear boundaries, and the weight of the tumors varied greatly, ranging from 7-990 g. The texture of the tumor was mostly soft or tough, and only 1 case exhibited a hard mass. Microscopically, most of the tumors were consistent with AGN, which consisted of mature ganglion cells, nerve fibers, spindle cells, and a myxoid matrix. For some cases that could not be clearly diagnosed, we performed immunohistochemistry examination, revealing a positive rate of 91.7% (11/12) for S-100 and 77.8% (7/9) for vimentin.

Discussion

AGN is a very rare tumor, and several studies have shown that the incidence of AGN in adre-

Table 3. Perioperative and follow-up results of 51 AGN patients

Variable	Value
Therapy	
Laparoscopic, n (%)	32 (62.8)
Open, n (%)	19 (37.2)
Operation time, median (range), min	141 (95-210)
Estimated blood loss, mean (range), ml	237.4 (50-800)
Postoperative complications, n (%)	9 (17.6)
Fever	5 (9.80)
Infection	2 (3.90)
Hypotension	2 (3.90)
Postoperative hospital stay, mean (SD), day	5.7 (1.3)
Follow-up, median (range), month	51.1 (2-125)

Note: AGN: Adrenal ganglioneuroma; SD: Standard deviation.

nalectomy specimens is < 2.0% [11, 12]. In this study, the incidence of AGN in our center was approximately 2.74%, which was slightly higher than the incidence reported in the literature. To the best of our knowledge, this study includes the largest number of cases among current studies on AGN. Unlike neuroblastoma, AGN is more common in adults and less common in children. Previous studies have shown that the age of onset of AGN is between 30 and 50 years, with no significant difference in incidence between men and women [13, 14]. The mean age at diagnosis of the 51 patients in this study was 41.2 years, which was generally consistent with the literature. In addition, the number of male patients in this study was 1.42-fold that of female patients, which is slightly different from reports in the literature. Because AGNs are benign tumors, patients generally do not have symptoms. However, given the insidious nature of the tumor's onset, the tumor may not be detected until it is quite large. When the tumor presses on surrounding tissues or organs, the patient develops low back pain or discomfort. According to statistics, 60-70% of cases are identified incidentally without any symptoms [15, 16]. Approximately 62.8% of the patients in this study had no symptoms, which was generally consistent with that reported in the literature. Given that AGN originates in the adrenal medulla, a small number of patients may experience elevated hormone levels. In this study, only 2 patients exhibited elevated hormone levels.

The CT findings of AGN are similar to those of other benign adrenal tumors. Given the low invasiveness of tumors, invasion of surrounding tissues or organs is generally not observed. The tumor typically exhibits a regular appearance, and the boundary is usually clear. Intratumoral calcification and cystic degeneration were observed. The tumor density on plain scans is generally lower than that of the psoas major, and the average CT value is generally 30 HU and less than 40 HU [17]. This characteristic of AGN is related to its histologic composition. If the tumor contains a large amount of myxoid matrix but relatively few cellular components, the CT value is generally less than 30 HU. In contrast, if the proportion of cellular components increases, the CT value of the tumor may be greater than 30 HU [18]. The mean CT value of the tumor in this study was 29.9±4.3 HU, which was generally consistent with that reported in the literature. The myxoid matrix of the tumor impedes the absorption and excretion of contrast material such that enhanced scans can exhibit delayed progressive enhancement, which is one of the features of the CT findings of AGN [19, 20]. Only 40 of the 51 patients in this study underwent enhanced CT scans, and 62.5% of the tumors had delayed progressive enhancement, indicating that this feature contributed to the diagnosis of AGN.

Although enhanced CT scans have guiding significance in the diagnosis of AGN, this feature is not specific. Thus, the final diagnosis still depends on histology. It is not difficult to confirm AGN based on a histologic perspective. Microscopically, well-differentiated ganglion cells, nerve fibers, and spindle cells, and a large amount of myxoid matrix can be observed. If the diagnosis is not confirmed by H&E staining, immunohistochemistry is needed for diagnosis. S-100 and NSE are often positive, and the diagnosis of AGN can generally be made when combined with the results of H&E staining [21, 22].

The benign biological behavior of AGNs determines their good prognosis. As with other benign adrenal tumors, surgical resection of the tumor represents the most effective treatment. In this study, all 51 patients underwent adrenalectomy. After long-term follow-up, all patients achieved a good prognosis, and no tumor recurrence or metastasis occurred, which was generally consistent with other studies [23]. Nonetheless, it is not clear which sur-

Table 4. Comparison between laparoscopic and open adrenalectomy

Variable	Laparoscopic (n=32)	Open (n=19)	*p* value
Tumor size on pathology, median (range), cm	4.6 (2-12)	8.4 (2.5-10)	<0.001
Tumor weight, median (range), g	111.6 (7-990)	376.4 (11-790)	<0.001
Operation time, median (range), min	142.0 (100-210)	141.3 (95-185)	0.926
EBL, median (range), ml	191.7 (50-500)	314.4 (75-800)	0.027
Postoperative hospital stay, median (range), day	5.59 (3-8)	6.10 (4-8)	0.160
Postoperative complications, n (%)	4 (12.6)	5 (26.3)	0.383

Note: EBL: Estimated blood loss.

Table 5. Comparison of clinical data based on tumor size

Variable	<6 cm (n=23)	≥6 cm (n=28)	*p* value
Tumor weight, median (range), g	59.6 (7-303)	334.0 (81-990)	<0.001
Operation time, median (range), min	122.8 (95-155)	157.3 (120-210)	<0.001
EBL, median (range), ml	117.3 (50-220)	336.0 (150-800)	<0.001
Postoperative hospital stay, median (range), day	5.2 (3-8)	6.2 (4-8)	0.005
Postoperative complications, n (%)	3 (13.0)	6 (21.4)	0.680

Note: EBL: Estimated blood loss.

Table 6. Pathologic findings of 51 AGN patients

Variable	Value
Tumor weight, median (range), g	210.2 (7-990)
Tumor texture	
Soft, n (%)	17 (33.3)
Tough, n (%)	33 (64.7)
Hard, n (%)	1 (2.0)
Immunohistochemistry	
S-100 positive, n (%)	11/12 (91.7)
Vimentin positive, n (%)	7/9 (77.8)

Note: AGN: Adrenal ganglioneuroma.

gical method should be chosen to remove the tumor. In general, laparoscopic adrenalectomy is the preferred surgical method for adrenal gland tumors less than 6 cm in diameter, whereas open adrenalectomy exhibits better efficacy and safety for those greater than 6 cm. However, because AGN is so rare, few studies have compared the efficacy and safety of laparoscopic adrenalectomy versus open adrenalectomy in the treatment of AGN. Our results showed that the EBL was lower in the laparoscopic group. However, this finding may be related to the smaller tumor size in the laparoscopic group given that we tend to prefer laparoscopic resection of small tumors and open surgery for large tumors. A surgical decision based exclusively on the size of the tumor may not be correct given the relationship between the tumor and the surrounding tissue as well as the potential for malignancy. In this study, the largest tumor resected by laparoscopy was 12 cm in diameter, indicating that laparoscopic adrenalectomy is feasible for large AGNs. Although tumor size is not the sole determinant of surgical procedures, it can influence the perioperative outcome. According to this study, larger tumors may lead to greater EBL and longer postoperative hospital stays, so greater care should be taken during surgical resection of large AGNs.

Our study has several limitations. First, this study is a retrospective study, which may cause bias in the data. Second, only CT was used for the preoperative diagnosis of patients, and MRI was not used. Finally, although this report involves the largest AGN series to date, the number of cases included is still small. Thus, the reliability of the results may be affected.

Conclusion

This study reports the largest series of AGNs to date. We comprehensively described AGN in terms of demographics, clinical manifestation, imaging and histologic features, and analyzed the impact of different surgical methods and tumor size on perioperative outcome. Our study will deepen the understanding of AGN among

clinicians and provide guidance for the diagnosis and treatment of AGN. We expect more cases to be reported in the future. In addition, more accurate preoperative diagnosis methods need to be developed to improve the preoperative diagnosis rate of AGN.

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Disclosure of conflict of interest

None.

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References

[1] Lonergan G, Schwab C, Suarez E and Carlson C. Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma: radiologic-pathologic correlation. Radiographics 2002; 22: 911-934.

[2] Lee J, Chai Y, Kim T, Choi J, Lee K, Kim H, Yoon Y and Kim H. Clinicopathological features of ganglioneuroma originating from the adrenal glands. World J Surg 2016; 40: 2970-2975.

[3] Mylonas K, Schizas D and Economopoulos K. Adrenal ganglioneuroma: what you need to know. World J Clin Cases 2017; 5: 373-377.

[4] Shimada H, Ambros I, Dehner L, Hata J, Joshi V and Roald B. Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. Cancer 1999; 86: 349-363.

[5] Fliedner S, Winkelmann P, Wesley R, Vonthein R and Lehnert H. Ganglioneuromas across age groups: systematic review of individual patient data. Clin Endocrinol 2021; 94: 12-23.

[6] Geoerger B, Hero B, Harms D, Grebe J, Scheidhauer K and Berthold F. Metabolic activity and clinical features of primary ganglioneuromas. Cancer 2001; 91: 1905-1913.

[7] Okamatsu C, London W, Naranjo A, Hogarty M, Gastier-Foster J, Look A, LaQuaglia M, Maris J, Cohn S, Matthay K, Seeger R, Saji T and Shimada H. Clinicopathological characteristics of ganglioneuroma and ganglioneuroblastoma: a report from the CCG and COG. Pediatr Blood Cancer 2009; 53: 563-569.

[8] Hayashi Y, Iwato M, Hasegawa M, Tachibana O, von Deimling A and Yamashita J. Malignant transformation of a gangliocytoma/ganglioglioma into a glioblastoma multiforme: a molecular genetic analysis. Case report. J Neurosurg 2001; 95: 138-142.

[9] Maweja S, Materne R, Detrembleur N, de Leval L, Defechereux T, Meurisse M and Hamoir E. Adrenal ganglioneuroma. A neoplasia to exclude in patients with adrenal incidentaloma. Acta Chir Belg 2007; 107: 670-674.

[10] Iacobone M, Torresan F, Citton M, Schiavone D, Viel G and Favia G. Adrenal ganglioneuroma: The Padua Endocrine Surgery Unit experience. Int J Surg 2017; 41 Suppl 1: S103-S108.

[11] Kasperlik-Zaluska A, Roslonowska E, Slowinska-Srzednicka J, Otto M, Cichocki A, Cwikla J, Slapa R and Eisenhofer G. 1,111 patients with adrenal incidentalomas observed at a single endocrinological center: incidence of chromaffin tumors. Ann N Y Acad Sci 2006; 1073: 38-46.

[12] Xie J, Dai J, Zhou W and Sun F. Adrenal ganglioneuroma: features and outcomes of 42 cases in a Chinese population. World J Surg 2018; 42: 2469-2475.

[13] Qing Y, Bin X, Jian W, Li G, Linhui W, Bing L, Huiqing W and Yinghao S. Adrenal ganglioneuromas: a 10-year experience in a Chinese population. Surgery 2010; 147: 854-860.

[14] Linos D, Tsirlis T, Kapralou A, Kiriakopoulos A, Tsakayannis D and Papaioannou D. Adrenal ganglioneuromas: incidentalomas with misleading clinical and imaging features. Surgery 2011; 149: 99-105.

[15] Xiao J, Zhao Z, Li B and Zhang T. Primary retroperitoneal ganglioneuroma: a retrospective cohort study of 32 patients. Front Surg 2021; 8: 642451.

[16] Koktener A, Kosehan D, Akin K and Bozer M. Incidentally found retroperitoneal ganglioneuroma in an adult. Indian J Surg 2015; 77: 3-5.

[17] Zhang Q, Song T, Yang P and Hao Q. Retroperitoneum ganglioneuroma: imaging features and surgical outcomes of 35 cases at a Chinese institution. BMC Med Imaging 2021; 21: 114.

[18] Otal P, Mezghani S, Hassissene S, Maleux G, Colombier D, Rousseau H and Joffre F. Imaging of retroperitoneal ganglioneuroma. Eur Radiol 2001; 11: 940-945.

[19] Guan Y, Zhang W, Zeng Q, Chen G and He J. CT and MRI findings of thoracic ganglioneuroma. Br J Radiol 2012; 85: e365-372.

[20] Shawa H, Elsayes K, Javadi S, Morani A, Williams M, Lee J, Waguespack S, Busaidy N, Vassilopoulou-Sellin R, Jimenez C and Habra M. Adrenal ganglioneuroma: features and out-

comes of 27 cases at a referral cancer centre. Clin Endocrinol 2014; 80: 342-347.
[21] Bin X, Qing Y, Linhui W, Li G and Yinghao S. Adrenal incidentalomas: experience from a retrospective study in a Chinese population. Urol Oncol 2011; 29: 270-274.
[22] Jain M, Shubha B, Sethi S, Banga V and Bagga D. Retroperitoneal ganglioneuroma: report of a case diagnosed by fine-needle aspiration cytology, with review of the literature. Diagn Cytopathol 1999; 21: 194-196.
[23] Luo L, Zheng X, Tao K, Zhang J, Tang Y and Han F. Imaging analysis of ganglioneuroma and quantitative analysis of paraspinal ganglioneuroma. Med Sci Monit 2019; 25: 5263-5271.