

Table 2: Endocrine

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
Cozzi et al (2009) ¹	<p><u>Study Design:</u> Prospectively followed case series.</p> <p><u>Patient Population:</u> Seventy-two adult patients who underwent transsphenoidal resection of NFPA.</p> <p><u>Study Description:</u> To evaluate the need for postoperative steroids in patients with NFPA.</p> <p>Cortisol level was measured at 08:00 before surgery and on POD#2. All other hormone levels were measured as well.</p> <p>Patients with pre-op hypocortisolism received steroids before surgery. If POD#2 cortisol was normal, patients did not receive steroids.</p> <p>Patients were re-evaluated for glucocorticoid and other hormonal requirements at 6 weeks and then after 12 months. Those with DI were evaluated 3 months and 12 months post-op.</p>	Clinical Assessment / III	<p><u>Results:</u></p> <p>Fourteen patients had pre-op hypocortisolism.</p> <p>One out of 14 showed improvement of the hypocortisolism postoperatively.</p> <p>Six out of 58 patients with normal preoperative cortisol developed post-op hypocortisolemia.</p> <p>In all but 1 patient, the normal cortisol level on POD#2 was confirmed at 6-week tests.</p> <p>At 1 year follow-up all patients with normal cortisol level on POD#2 demonstrated normal cortisol level, and the stimulation test at 1 year confirmed the results of cortisol stimulation test performed 6 weeks post-op.</p> <p>DI occurred in 10 patients postoperatively and was permanent in 3.</p> <p>All these data were confirmed with LFACTH test.</p> <p><u>Authors' Conclusions:</u></p> <p>A simple 08:00 h evaluation of free cortisol level in pre-op and on POD#2 postop should suffice to assess HPA function.</p> <p>Suggest that perioperative steroid treatment should be reserved for patients with low level of pituitary cortisol.</p>

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			<p>The value of free cortisol on POD#2 should guide the need for future prescription of post-op glucocorticoid replacement.</p> <p><u>Comments:</u></p> <p>This is a prospective follow-up study and not a comparative study. The authors did not report whether patients with postoperative hypocortisolemia ever showed improvement of this function. Furthermore, while they mention the occurrence of DI in the postoperative period, they do not give any data on the immediate and long-term evaluation of this function. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.</p>
Colao et al (1998) ³	<p><u>Study Description:</u> Retrospective analysis.</p> <p><u>Patient Population:</u> 84 adult patients with NFPA.</p> <p><u>Study Design:</u> Evaluate the endocrine and ophthalmologic effects of surgery followed by RT in patients with NFPA.</p> <p>Follow-up duration was 1 year for all 84 patients, 2-5 years in 63 patients, 6-10 years in 32 patients, and 16 patients were followed for more than 10 years.</p>	Clinical Assessment / III	<p><u>Results:</u></p> <p>sixty-two out of 84 presented with hypopituitarism.</p> <p>Sixteen patients maintained normal pituitary function immediately after surgery, 8 patients improved, and 34 worsened.</p> <p>In 59 patients who received RT 6-12 months after surgery, notable impairment of pituitary function was noticed 2.5 years post RT. Prevalence increased from 28.8% 1 year post RT to 92% after more than 10 years after RT.</p> <p><u>Authors' Conclusions:</u></p>

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	<p>All 84 patients underwent surgical resection; 72 patients with residual tumor were considered for RT, but 13 refused.</p> <p>Endocrine function was assessed pre-op, then 1-3 months post-op, then quarterly in the first year and yearly after that.</p> <p>Ophthalmologic and radiologic follow-up was performed as well.</p>		<p>Long-term endocrinologic follow-up should be carried out in patients with NFPA who have undergone surgery and RT.</p> <p><u>Comments:</u></p> <p>The authors do not directly address the follow-up schedule for patients with NFPA who undergo surgery and RT. Nevertheless, from the data presented, we can extrapolate that due to the high incidence of pituitary insufficiency presenting more than 10 years after treatment, long-term endocrine follow-up is needed. Concordance index between observers for the conclusions reached was not reported.</p>
Chen et al (2011) ⁴	<p><u>Study Design:</u> Prospectively followed case series.</p> <p><u>Patient Population:</u> 385 patients with NFPA followed prospectively.</p> <p><u>Study Description:</u> This large cohort of patients was followed prospectively in order to determine the preoperative and postoperative endocrine status of patients operated on for NFPA. Electrolytes and hormones were assessed postoperatively and at 6 weeks, and as needed thereafter.</p>	Clinical Assessment / III	<p><u>Results:</u></p> <p>Postoperatively, GH deficiency was present in 49.1% of patients, hypogonadism in 33.2%, and hypoprolactinemia in 14.8%.</p> <p>Hypocortisolism was confirmed in 84 (21.8%) patients with abnormal POD#2 08:00 serum cortisol level. They were given glucocorticoid replacement. On POD#6, low serum cortisol was detected in 122 (31.7%) patients, and they were discharged on glucocorticoid replacement.</p> <p>Hypothyroidism was seen in 135 (35.1%) of patients who were given levothyroxine replacement.</p> <p>At 6 weeks, 87 patients had hypocortisolism and 67 had hypothyroidism. At 3, 6, and 12 months, testing revealed normalization in all except 8 patients. These patients were continued in permanent hormonal replacement.</p>

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			<p>Only patients with pituitary apoplexy or cortisol deficiency received preoperative cortisol replacement.</p> <p>Hyponatremia was evident in 22.1% of patients and improved at discharge or within 6 weeks.</p> <p>18.7% had DI postoperatively; this decreased to half by discharge and to 0.8% permanently.</p> <p><u>Authors' Conclusions:</u></p> <p>Postoperative endocrine deficiency was common; up to 1/3 had steroid or thyroid deficiency. Appropriate follow-up of endocrine function is important to determine the need and the length of time for hormonal replacement.</p> <p><u>Comments:</u></p> <p>Not a randomized study. Endocrine follow-up to determine the need for hormonal replacement is recommended from these results. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.</p>
Berkmann et al (2014) ¹⁹	<p><u>Study Design:</u> Retrospective case series.</p> <p><u>Patient Population:</u> 210 patients with NFPA.</p>	Clinical Assessment / III	<p><u>Results:</u></p> <p>Overall, 73% of patients had an element of hypopituitarism preoperatively; this continued in 64% of patients on last follow-up.</p> <p>One-third of the patients already showed recovery of pituitary function within 10 days after surgery.</p>

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	<p><u>Study Description:</u> Patients underwent surgery for initial NFPA in iMRI suite and radiologic, endocrinologic, and visual sequelae were tracked with a mean follow-up of 5 years.</p> <p>Endocrine testing was performed preoperatively and 7 days and 3 months postoperatively and then yearly for at least 3 years.</p>		<p>Fifty percent showed some degree of recovery at 3 months.</p> <p>At 12 months, another 11% of patients showed recovery of some pituitary axis. New pituitary deficits were found in 26% of the patients.</p> <p>In total, 66% of patients experienced some degree of pituitary function recovery.</p> <p>This did not correlate with iMRI-guided resection or GTR.</p> <p><u>Authors' Conclusions:</u></p> <p>One-third of the patients already showed recovery of pituitary function within 10 days after surgery. This recovery may continue for at least 12 months; re-testing after several months may be reasonable to avoid possible lifelong hormone substitution therapy.</p> <p><u>Comments:</u></p> <p>The authors conclude that endocrinologic function may continue to improve, but they do not define the maximal length of time needed for this recovery. Concordance index between observers for the conclusions reached was not reported.</p>
Pollock et al (2008) ²⁰	<p><u>Study Description:</u> Retrospective case series.</p>	Clinical Assessment / III	<p><u>Results:</u></p> <p>Imaging and endocrinologic follow-up data were typically obtained at baseline, 6-month intervals after radiosurgery for the first 2 years, and yearly thereafter.</p>

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	<p><u>Patient Population:</u> Sixty-two patients primarily and with recurrent NFPA underwent gamma knife radiosurgery.</p> <p><u>Study Design:</u> Radiographic and endocrinologic data were obtained in only 41 of 62 patients after GK RT, with a median follow-up of 69 +/- 32 months. Thirty-four patients were followed at 3 years, and 16 were followed for more than 6 years.</p>		<p>New hypopituitarism developed in 11 (27%) of the 41 patients. They were detected at a median of 12 months post RT.</p> <p>The actuarial risk of developing new hypopituitarism at 5 years was 32%.</p> <p>Five-year risk of developing new anterior pituitary deficits was 18% for patients with a tumor volume of <4.0 cm³, compared with 58% for patients with a tumor volume >4.0 cm³.</p> <p><u>Authors' Conclusions:</u></p> <p>A primary complication of GK is hypopituitarism, and the risk of developing new anterior pituitary deficits correlates with the size of the irradiated tumor and bears longer-term hormonal testing.</p> <p><u>Comments:</u></p> <p>The paper does not specifically address follow-up schedules for patients with NFPA after GK radiation. Nevertheless, from the data, we can extrapolate that due to the risk of pituitary dysfunction, long-term endocrinologic follow up is needed in these patients. Concordance index between observers for the conclusions reached was not reported.</p>
Tominaga et al (1995) ²¹	<p><u>Study Design:</u> Retrospective analysis</p> <p><u>Patient Population:</u> Thirty-three adult patients with NFPA.</p>	Clinical Assessment / III	<p><u>Results:</u></p> <p>Pre-op evaluation showed impairment of GH in 30 patients, LH in 16, ACTH in 15, FSH in 13, TSH in 6, and PRL in 2. Hyperprolactinemia was found in 13 patients.</p>

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	<p><u>Study Description:</u> Thirty-three patients who had >10 years follow-up after surgical treatment and RT. Thirty-three patients underwent surgical resection (14 total adenomectomy, 12 subtotal, and 7 partial). Post-op RT was performed in 8 patients. RT was started 1 month after surgery.</p> <p>Pituitary function was evaluated preoperatively, then at 2 weeks, 3 months, 6 months, 1 year post-op, and then annually. In patients who underwent RT post-op, it was done at 2 week post-op, then 2 months, 5 months, and 1 year post RT and then annually.</p>		<p>85% of patients whose function was restored reached this stage within the first 3 months postoperatively, but it took 3 months to 1 year for the others.</p> <p>There was no improvement noticed after 1 year.</p> <p>In patients in whom total resection was performed, there was no impairment of pituitary function seen.</p> <p>In patients who underwent subtotal resection, some developed recurrence of pituitary hormonal dysfunction secondary to regrowth.</p> <p>In patients who underwent only partial resection, impairment of pituitary function occurred after 1 year irrespective of tumor regrowth.</p> <p>Patients who underwent RT developed impairment of anterior pituitary function 8-9 years after RT, and 2 patients even after 11 years.</p> <p><u>Authors' Conclusions:</u></p> <p>Endocrinological follow-up schedule should be decided based on the initial treatment of NFPA:</p> <ul style="list-style-type: none"> - Patients who undergo total resection of tumor can be exempted from periodic endocrinologic follow-up after 1 year if pituitary function is normalized. - Patient with non-curative surgery and especially those undergoing RT require endocrinologic examination for at least 11 years.

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			<p><u>Comments:</u></p> <p>Retrospective study. The authors did not compare different follow-up schedules to find the best algorithm for post-treatment endocrine evaluation. Furthermore, the authors did not study how different follow-up modalities and radiologic, endocrinologic, and ophthalmologic evaluation could be combined for best results. Nevertheless, due to reported occurrence of hypopituitarism after 11 years, long-term endocrine follow-up in this patient population is recommended. Concordance index between observers for the conclusions reached was not reported.</p>
Hensen et al (1999) ²³	<p><u>Study Design:</u> Prospectively followed case series.</p> <p><u>Patient Population:</u> 1571 adult patients with pituitary adenoma, among whom 534 had NFPA.</p> <p><u>Study Description:</u> Urine output and serum sodium was monitored for 10 days after surgery, then 3 months after surgery for 24 hours, then 1 year post-op for 24 hours. These patterns were defined: (1) immediate polyuria—occurring day 1-3 post-op without hyponatremia; (2) prolonged polyuria—occurring day 1-7 post-op without</p>	Clinical Assessment / III	<p><u>Results:</u></p> <p>Of 534 patients with NFPA, 138 (26%) suffered immediate postoperative polyuria (pattern 1), 51 (10%) developed prolonged polyuria (pattern 2), 18 (3%) developed postoperative hyponatremia (Na <132 mmol/L) (pattern 3), 17 (3%) delayed hyponatremia (pattern 4), 20 (4%) had a biphasic pattern (pattern 5), and 8 (1%) had showed a triphasic pattern (pattern 5) of polyuria and hyponatremia.</p> <p>Patients were treated with fluid restriction, a salt-rich diet, and oral sodium supplementation.</p> <p><u>Authors' Conclusions:</u></p> <p>Patients with NFPA are at risk of developing postoperative polyuria and hyponatremia. Large amounts of fluids or IV administration of hypotonic fluids should be avoided between 4 and 9 days post-op.</p>

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	<p>hyponatremia; (3) immediate post-op hyponatremia with or without immediate polyuria (day 1-3); (4) isolated delayed hyponatremia without polyuria; (5) biphasic course—immediate post-op polyuria, day 1-3 followed by hyponatremia; (6) triphasic course—prolonged polyuria (>7 days) with hyponatremic episodes.</p>		<p><u>Comments:</u></p> <p>This is not a randomized controlled trial. According to the data reported by the authors, postoperative hyponatremia with or without polyuria can occur within the first 3 days or after 7 days, suggesting follow-up of serum sodium levels at these intervals. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.</p>