Abstract: Pheochromocytoma is a tumor that arises from adrenal medulla and it is characterized by increased secretion of catecholamines. The incidence of pheochromocytoma is 3 to 8 cases per million inhabitants, of which about 10 to 20% of diagnosed pheochromocytomas occurs in the pediatric population, with a higher frequency in boys. In 1.7% of the pediatric population with hypertension, the cause of hypertension is pheochromocytoma. Due to headaches and verified hypertension on twenty-four-hour holter blood pressure monitoring, the 13-year-old female patient underwent ultrasound, followed by scintigraphy and magnetic resonance imaging of the abdomen, which described an oval change above the right kidney about 4.5 cm in diameter suspected of pheochromocytoma. Twenty-four-hour urine cateholamines showed elevated noradrenaline values as much as 45 times higher than the reference range, as well as elevated dopamine values. After adequate preparation with phenoxybenzamine and bisoprolol for two weeks, a right laparoscopic adrenalectomy was performed at the University Children’s Clinic in Tirsova, which is also the first operation of this type in the pediatric population. Intraoperatively, the maximum value of tension was 180/120 mmHg. Pathohistological findings confirmed pheochromocytoma. Although a rare cause of hypertension in the pediatric population, young
patients with newly diagnosed hypertension should be examined for possible pheochromocytoma. Laparoscopic adrenalectomy through both the lateral transabdominal and posterior retroperitoneoscopic approach is the gold standard for the treatment of pheochromocytomas in both the adult and pediatric populations.

**Introduction**

Pheochromocytoma (PHEO) is a rare, neuroendocrine tumor that arises from the adrenal medulla, and is manifested by oversecretion of catecholamines (adrenaline, noradrenaline, and/or dopamine) (1, 2). The annual global incidence rate is around 2-9 per 1 000 000 inhabitants in general population (2). Clinical signs and symptoms of PHEO include conditions that catecholamine excess leads to, primarily – hypertension (80.7%), headache (60.4%), palpitations (59.3%), diaphoresis (52.4%), and, in lesser extent, fatigue, weight loss, flushing, abdominal pain and hyperglycemia. Because of highly unspecific symptomatology of PHEO, clinical diagnosis can be made extremely difficult considering the broad spectrum of differential diagnoses (extra adrenal paragangliomas, anxiety disorders, essential hypertension, hyperthyroidism, carcinoid syndromes, and many others), which is why PHEO is often referred to as the “Great Mimic” (2).

If there is a clinical suspicion of PHEO, the diagnosis is confirmed by a combination of laboratory analyses (catecholamines and metanephrines in 24-hour urine assessment) and anatomical imaging (echosonography, multislice computed tomography (MSCT), magnetic resonance imaging (MRI)), as well as much important functional imaging, such as scintigraphy with \textsuperscript{123}I-MIBG as radiopharmaceutical of choice, where in PHEO the expected finding is intense accumulation of radiopharmaceutical in adrenal region (2).

10–20% of PHEO is diagnosed in pediatric age, and is showed that 1.7% of children with hypertension has a PHEO as an underlying cause. In pediatric population, median age for diagnosing PHEO is 11–13 years, with predominance in boys, by some authors even as much as 2:1 (1, 2). Methodology of diagnostic is for the most part unchanged compared to adult population, but genetic screening and elaborate diagnostics should be taken with goal of ruling out PHEO-associated syndromes (Von Hippel-Lindau (VHL) syndrome, Multiple endocrine neoplasia (MEN) 2A and 2B syndromes and neurofibromatosis type 1 (NF1)) (1).

In this paper we present first case of elective laparoscopic adrenalectomy in patient with clinically manifested pheochromocytoma in pediatric age in University Children’s Hospital – Tiršova.
Case presentation

Female patient aged 12 + 10/12, with body height of 166 cm and body weight of 55.8 kg is admitted to hospital for evaluation of flushing of the cheeks and frequent headaches. 2 years prior to the hospitalization the patient had metformin introduced because of elevated fasting glycemia. During the hospitalization it was noted that headaches were always followed by blood pressure (BP) elevation, which is why holter monitoring of BP was indicated. On 24-hour BP holter monitor, 96% of all registered BP values were over 135/85 mmHg. Afterwards, an abdominal ultrasound was conducted which revealed a solid oval nodule 4.5x4.8 cm in diameter on top of the upper pole of the right kidney. Later on, MRI confirmed a hyperintense nodular mass 4.5 cm in diameter in region of right adrenal gland (Image 1). Due to clinical signs, as well as visualized adrenal mass, a whole body scintigraphy was performed, cateholamine and metanephrine assessment in 24-hour urine sample. Scintigraphy showed intense accumulation of radiopharmaceutical in right adrenal region (Image 2). Elevated values of noradrenaline were detected in two 24-hour urine samples, as well as elevated dopamine values in one of the samples (Table 1). Cortisol and ACTH were in reference range. Considering the results of the whole diagnostic procedure mentioned above, the diagnosis of PHEO was confirmed, indicating surgical treatment after adequate preoperative pharmacological preparation with phenoxybenzamine and bisoprolol in duration of 2 weeks. Surgical treatment was then undertaken in University Children’s Hospital - Tīšova and right laparoscopic adrenalectomy was performed by lateral transperitoneal approach (LTA). Intraoperatively, the highest BP value was 180/120 mmHg. For intraoperative BP control sodium-nitroprusside was used. Postoperative course went well, and patient was discharged from the hospital by the fourth postoperative day. Pathohistological finding confirmed PHEO. BP on the first follow-up, a month after surgical treatment was 105/65 mmHg. Gene testing bloodwork was conducted - currently pending.

Discussion

First successful surgical treatment in patients with PHEO was undertaken by Cesar Roux (1857–1934) in Switzerland, as well as Charles Horace Mayo (1865–1939) in the USA in 1926. (3). Laparoscopic adrenalectomy (LA) has been a golden standard in PHEO treatment ever since 1992. when a paper by Michael Gagner was published, in which the first three successful laparoscopic adrenalectomies were presented by using laparoscopic lateral transperitoneal approach (LTA) (4). Other than the mentioned approach, the LA can be done by using frontal transperitoneal, as well as retroperitoneal approach.
In Center for Endocrine Surgery, University Clinical Center of Serbia LTA is being used as routine procedure since 2012. LA is especially indicated for functional tumors which are smaller in size, as well as afunctional tumors, for which the chance for malign alteration has been identified as minimal (5, 6). As per every method, LTA is not without flaws. Absolute contraindications include tumors with over 15 cm in diameter, local tumor invasion, suspected adrenocortical carcinoma (ACC) and metastatic PHEO, while the relative containdications include increased cardiopulmonary risk as well as persistent coagulopathy (7–9). Maintaining intraoperative haemodynamic stability during the operation presents a challenge, which is why comparing haemodynamic stability during laparoscopic versus open approach (OA) surgery provides a constant cause for research on this topic, with results that don’t show statistically significant difference in incidence and degree of haemodynamic instability, length of operation and loss of blood between these two approches (9–14). Kim et al. (15) came to conclusion that the percentage of patients with intraoperative hypertensive crisis is lower in patients operated with LTA compared to OA (0.6 ± 0.5% during LTA and 1.67 ± 1.1% during OA, p = 0.0146). This study also showed faster postoperative oral intake in patients in LTA group (1.1 ± 0.3 days) compared to the OA group (2.6 ± 1.3 days, p = 0.0037). Also, there was a statistically significant difference in the length of poostoperative hospital stay (LTA 5.6 ± 2 days, OA 12.4 ± 3.5 days, p = 0.0001), which was also confirmed by Miccoli et al. (16) (4.1 ± 2.3 days in LTA, 7.2 ± 2.6 in OA, p < 0.02). Miccoli’s team also compared the length of the very intervention, showing longer length of the intervention for LTA (182 ± 115 minutes) compared to the OA (142 ± 29 minutes, p < 0.02). In addition, the need for analgesics usage was shown to be lower after LTA. Comparing the length of LA between hormone producing tumors and incidentalomas Cheah et al. showed that procedures were slightly longer in patients without symptoms of hormone overproduction (193 (130–340) minutes) compared to 182 (90–305) minutes in patients with confirmed syndromes associated with adrenal tumors (17). The average blood loss during the laparoscopic operation varies greatly among different papers with Miccoli et al. (16) showing a loss of average 342 mL and Janetschek et al. (18) showing a loss of average 130 mL of blood. The difference of volume of blood lost, the percentage of conversion of LA into OA mid-procedure, length of postoperative hospital stay, tumor size and ASA score was shown to be not too different between PHEO and other adrenal tumors operated with laparoscopic approach (19–21).

The results of the case we presented match results of other authors that tackled this topic, especially in terms of postoperative oral intake which was started by the second postoperative day, as well as adequate pain control which was achieved with minimal doses of analgesics. The patient was discharged from the hospital on the third postoperative day, which also matches the data gained from earlier research.
Main intraoperative challenge during the PHEO operation, independent of the approach (LTA or OA), is identifying the adrenal vein. With OA, ligating the vein is doable after intraoperative tumor mobilization, which was shown in earlier research to be responsible for the occurrence of hypertensive crisis (22). It is with that idea that Fernandez-Cruz et al. (23) pointed out the advantages of laparoscopic approach for PHEO treatment 20 years ago, showing that LTA lowers intraoperative release of catecholamines with a high statistical significance, lowering in turn the risk for hypertensive crisis occurrence, something that was not unique to just this research (10, 24). Even if LTA makes adrenal vein visualization easier, in our experience, this can be made difficult because of the adjacent adipose tissue. LA of the clinically verified PHEO should be done by experienced endocrine surgery specialists, since the conversion from laparoscopic to OA occurs in about 2% of all cases, which is something that can only be done by surgeons also experienced in the open adrenalectomy (7). Main reasons for conversion could be, primarily uncontrolled bleeding, adhesions, patient obesity, adjacent organ injury, hepatomegaly or lack of surgeon’s experience. (7–9, 25, 26). Shen et al. showed BMI values of over 24 kg/m$^2$ and tumor size of over 5 cm to be good predictive factors for conversion to OA (25).

The case we present was, in fact, in high risk for conversion, and one of the bigger reasons it hasn’t come to it is because by the time the presented case was treated, over 100 adrenalectomies were performed in Center for Endocrine Surgery, University Clinical Center of Serbia by the use of LTA, both for PHEO, as well as other functional and non-functional adrenal tumors. Our experience also shows that LTA is linked with less frequent complications compared to the OA (wound infection, respiratory infections, lower intraoperative organ trauma incidence), which matches the referenced research (25–27).

**Conclusion:**

For decades, the development of minimally invasive techniques has radically changed the surgical approach to the routine treatment of the adrenal gland diseases, with intensive research continually proving the safety, efficacy and convenience of laparoscopic compared to the open approach, making the laparoscopic adrenalectomy the golden standard for adrenal tumor treatment. Provided the adequate preoperative pharmacological preparation is carried out, along with great intraoperative coordination of experienced surgical and anesthesiological teams, it can be deduced that laparoscopic adrenalectomy stands as the method of choice for the treatment of pheochromocytoma, in both adult and pediatric populations.
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Image 1. MRI showing hyperintense nodular mass in region of adrenal gland

Image 2. Scintigraphic finding of intense accumulation of radiopharmaceutical in adrenal region

Dg.: Pheochromocytoma lat. dex. suspect
### Table 1. Catecholamine values in 2 consecutive 24-hour urine samples

|                | I sample | II sample | Reference range |
|----------------|----------|-----------|-----------------|
| Adrenaline     | 58,2     | 9,5       | 180             |
| Noradrenaline  | 26632,1  | 4943,4    | 570             |
| Dopamine       | 6891,9   | 1430,5    | 3240            |
| Normetanephrine| 3,1      | 3,26      | 3,6             |