



Intracerebral haemorrhage as a first sign of pheochromocytoma: case report and review of the literature

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Abstract

Pheochromocytomas and sympathetic paragangliomas are rare catecholamine-secreting tumours that represent very rare causes of intracerebral haemorrhage in the young, with only a few cases reported.

A 32-year-old man presented to our emergency department because of sudden onset of severe headache. He had a six-month history of paroxysmal headache, palpitations, and sweating. During examination he became somnolent and developed left-sided hemiplegia. A computed tomographic (CT) scan of the brain showed a right temporoparietal haematoma. He was admitted to the Clinic for Neurosurgery and the haematoma was evacuated. The patient was comatose, on assisted respiration, with frequent hypertensive crises. An examination for possible secondary causes of hypertension was undertaken. Plasma metanephrine value was elevated (414 pg/mL, reference values < 90 pg/mL). Abdominal CT scans revealed a large mass (6 cm) in the right adrenal gland. After adequate control of the hypertension was achieved with nonselective α - and β -adrenergic blockers the tumour was excised. The histopathologic findings confirmed the diagnosis of pheochromocytoma. The genetic analysis demonstrated a duplication in exon 1 of the *VHL* gene.

We reported a rare, potentially fatal complication of pheochromocytoma — an intracerebral haemorrhage. This case and review of similar rare cases in the literature illustrate the importance of early recognition of the characteristic symptoms of catecholamine excess in young patients with hypertension. (*Endokrynol Pol* 2019; 70 (3): 298–303)

Key words: pheochromocytoma; intracerebral haemorrhage; pheochromocytoma crisis

Introduction

Intracerebral haemorrhage in the young is usually caused by arteriovenous malformations, cavernous angiomas, or hypertension, followed by cerebral venous thrombosis, eclampsia, and sympathomimetic drugs [1, 2]. Pheochromocytomas and sympathetic paragangliomas are rare catecholamine-secreting tumours and represent very rare causes of intracerebral haemorrhage in the young. These tumours usually manifest with paroxysms of hypertension, headache, palpitations, sweating, and pallor. Most cases are sporadic, but they may be part of hereditary syndromes in 40–70% of cases [3, 4].

Pheochromocytoma crisis is an endocrine emergency associated with significant mortality. It has been defined as the acute severe presentation of

catecholamine-induced haemodynamic instability causing end-organ damage or dysfunction [5, 6]. In rare patients, pheochromocytoma crisis may be the first clinical manifestation of the underlying tumour. The most common presentation of pheochromocytoma crisis is hypertensive crisis or catecholamine cardiomyopathy [6]. The recommended management of pheochromocytoma crisis includes the use of α -blockade, and surgical intervention should be deferred until medical stabilisation has been achieved [6].

Some cases of these catecholamine-secreting tumours presenting with intracerebral haemorrhage have been reported, two of them as autopsy cases [2, 7–15] (Tab. I). All these patients were young adults (except two children) and one patient had haemorrhagic stroke as the presenting feature of pheochromocytoma during pregnancy [7, 11, 14].



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We report a young male with adrenal pheochromocytoma presenting with intracerebral haemorrhage, and we perform a review of similar cases in the literature.

Case report

A 32-year-old male presented to the Emergency Department because of sudden onset of severe headache. He had had paroxysmal attacks of severe headaches, palpitations, sweating, nervousness, tremor, and abdominal pain over a six-month period. Blood pressure was never measured during these attacks. Four months before the presentation in the Emergency Department he had blurred vision and was examined by an ophthalmologist. Diagnosis of retrobulbar neuritis was made and the patient was treated with corticosteroids (prednisone 40 mg/day). During the examination in the Emergency Department, the patient became somnolent with a left-sided hemiplegia. Brain computed tomography (CT) scan revealed right temporoparietal haemorrhage (Fig. 1). A cerebral angiogram did not demonstrate a vascular anomaly. The patient was operated, and the intracerebral haematoma was evacuated. The postoperative period was complicated with hypertensive crisis. During crisis, the blood pressure was 240/160 mmHg, with a heart rate of 150 beats per minute, and the patient had hyperthermia (40°C) with sweating and tremor. The sudden onset of severe hypertension raised the suspicion of secondary hypertension, especially pheochromocytoma. Abdominal CT scan revealed a rounded mass of 6 cm in the right adrenal gland (Fig. 2). Plasma metanephrine value was elevated (414 pg/mL, reference values < 90 pg/mL). Routine laboratory test findings were within normal limits, urinalysis results were negative, and chest radiography was normal. Serum calcium level, parathormone, and calcitonin were within reference ranges. The diagnosis of pheochromocytoma was made, and non-competitive



Figure 1. Brain CT scan showing intracranial haemorrhage located in the right temporoparietal region

$\alpha 1/\alpha 2$ antagonist was initiated (phenoxybenzamine with a starting dose of 10 mg orally three times a day, increasing to 160 mg/d) and later β -blocker therapy was added (propranolol 80 mg/d). The patient was haemodynamically instable, with frequent hypertensive crises, and it took four months for adequate blood pressure control. During the preoperative period he developed severe complications (sepsis and deep venous thrombosis). After a waiting period of four months, during which the patient's condition stabilised, a right adrenalectomy was performed, with removal of the tumour of the right adrenal gland. Macroscopically, the tumour was dark brown, soft, with solid appearance on cross section. Tumour mass was 82 gr, with maximal diameter of 70 mm. The pathologic examination revealed a pheochromocytoma with a PASS score of 5

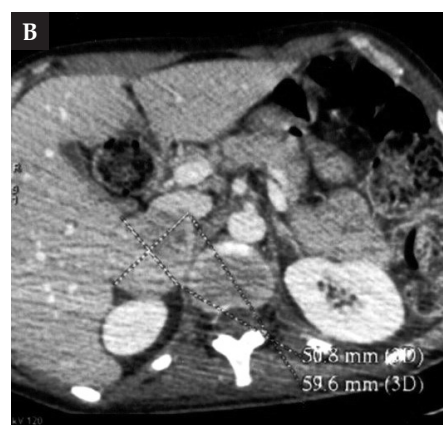


Figure 2AB. Abdominal CT scan showing a well-defined heterogenous mass in the region of the right adrenal gland

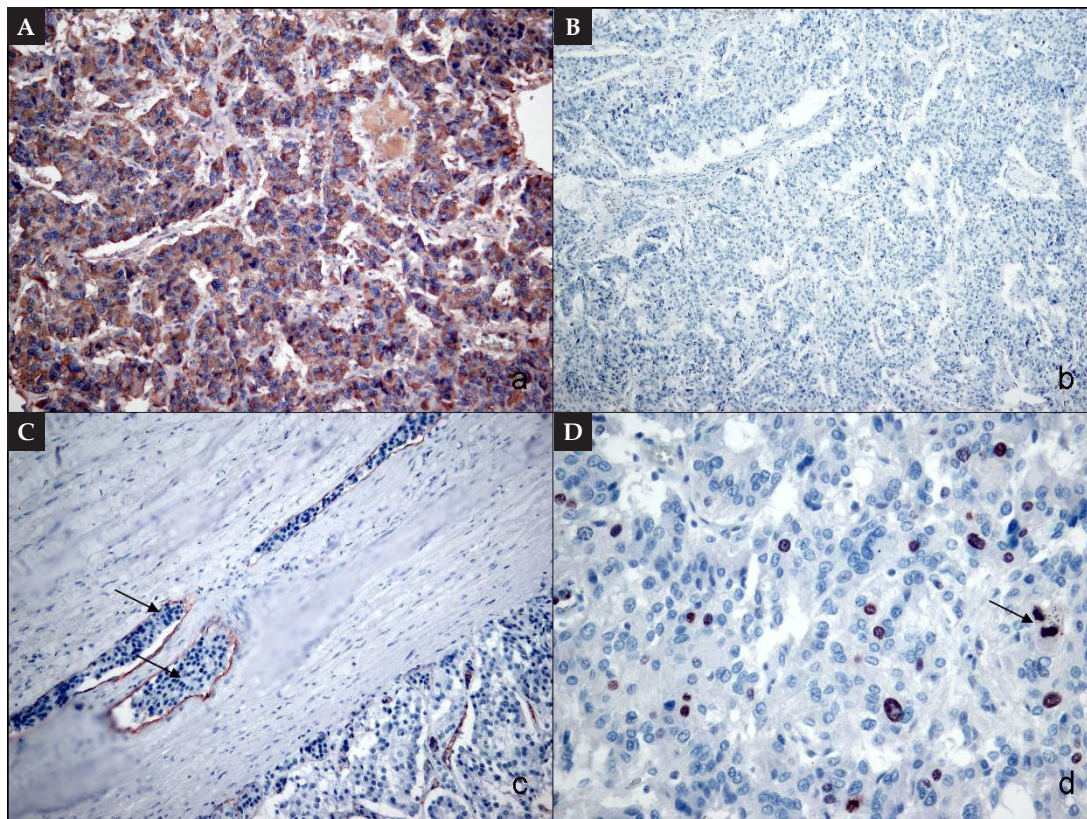


Figure 3. A. Diffuse granular cytoplasmic staining for chromogranin A (200×); B. Tumour cells were negative for melan A (200×); C. Vascular invasion (arrows); D. Atypical mitosis (arrow, Ki67 staining) (400×)

(eight mitoses on 10 high-magnification fields, atypical mitotic figures, with vascular invasion) (Fig. 3). Microscopically, the tumour was clearly encapsulated, with alveolar architecture, formed from medium-sized cells with amphophilic cytoplasm and with moderately polymorphic nuclei. Increased number and atypical mitoses were noticeable, as well as vascular invasion with the tumour (Fig. 3C and 3D). Immunohistochemically, the tumour cells were positive for chromogranin A and negative for melan A (Fig. 3A and 3B). Evidence for vascular invasion was obtained with CD31 staining for endothelial cells that line the vascular spaces (Fig. 3C).

Despite a negative family history, the occurrence of pheochromocytoma in a young patient strongly suggested the need for genetic analysis. Genetic testing was negative for germline mutations in *SDHB*, *SDHD*, and *VHL* genes. Multiplex ligation-dependent probe amplification (MLPA) showed duplication of exon 1 of the *VHL* gene. During the postoperative period and after the discontinuation of antihypertensive therapy, the patient was normotensive. Two months after right adrenalectomy, his condition improved, he was conscious, and with spontaneous respiration. Verbal communication was established, and the patient was sent for physical rehabilitation. The patient was followed for two years after adrenalectomy. He was normotensive

without antihypertensive therapy. Repeated blood analysis showed normal chromogranin A (87 ng/mL, reference values < 125 ng/mL). Urinary catecholamine levels were normal (adrenaline 2.3 µg/d, reference values < 20 µg/d; noradrenaline 9.3 µg/d, reference values < 105 µg/d; dopamine 60 µg/d, reference values < 450 µg/d). Ophthalmoscopy was normal, control abdominal CT scan was normal, and brain CT scan did not show intracranial lesions.

Discussion

Pheochromocytomas and sympathetic paragangliomas are rare neuroendocrine tumours that produce an excess of catecholamines, causing hypertension, headache, palpitations, sweating, tremor, and pallor. The annual prevalence is estimated to be about one or two per million persons [16]. These tumours may present in many ways, and they are known as the “disease with a thousand faces” [17]. Patients with pheochromocytomas/paragangliomas will often present with a history of poorly controlled or accelerated hypertension with symptoms (palpitations, headaches, inappropriate sweating, pallor, panic or anxiety attacks, abdominal pain, dyspnoea, weight loss) [17, 18]. Also, cyclic rapid fluctuation of hypertension and

Table I. Intracerebral hemorrhage in patients with pheochromocytoma / paragangliomas

Authors & Year	Sex (M/F)	Age at presentation (years)	Duration of symptoms prior diagnosis (years)	Neurological signs and symptoms	Tumor localization	Preoperative antihypertensive regimen	Genetic analysis
Moraca-Kvapilova et al., 1985	F	30	Diagnosed during pregnancy (35week)	Left hemiparesis, diaphoresis	Bilateral pheochromocytoma	Methyldopa + diuretics	<i>MEN 2A</i> Sy (clinical data)
Scardigli et al., 1985	F	24	7	Coma, quadriplegia	Pheochromocytoma	Phenoxybenzamine + metoprolol + metyrosine	NR
Aikawa et al., 2000	M	35	0	Coma	Pheochromocytoma	Autopsy report	NR
Moritani et al., 2001	M	51	3	Right hemiplegia	Bladder pheochromocytoma	Doxasocin + propranolol + amlodipine	NR
Chuang et al., 2002	M	6	0.5	Right hemiparesis, focal seizure	Pheochromocytoma	α , β and calcium channel blockers	NR
Park et al., 2006	M	18	2	Headache, left hemianopia	Paraganglioma in left paraaortic area	NR	NR
Douma et al., 2008	F	25	5	Dysarthria, right hemiparesis	Paraganglioma, pheochromocytoma	Phenoxybenzamine 30 mg/d + atenolol 25 mg/d	Negative for <i>RET</i> , <i>VHL</i> , <i>NF1</i> , <i>SDHB</i> , <i>SDHD</i>
Petramala et al., 2008	F	23	0.5	Left hemiplegia	Multiple paragangliomas	Doxazocin + propranolol + amlodipine	<i>SDHD</i>
Luiz et al., 2013	M	12	4	Headache, diaphoresis, left hemiparesis	Malignant paraganglioma (Zuckerkind)	NR	<i>SDHB</i>
Mizukami et al., 2013	F	30	3	Death	Bilateral pheochromocytoma	Autopsy report	NR
Our patient	M	32	0.5	Headache, palpitations, diaphoresis, left hemiplegia	Pheochromocytoma	Phenoxybenzamine 160 mg/d + propranolol 80 mg/d (4 months)	<i>VHL</i>

NR — not reported

hypotension, shock, ventricular dyskinesias, various electrocardiographic (ECG) abnormalities, and pulmonary oedema may comprise the initial presentation of catecholamine excess [19–21]. Very rarely, pheochromocytomas and paragangliomas may present with intracerebral haemorrhage, and some cases have been reported in adults and in the paediatric population [2, 7–15]. We reviewed these cases, with our case presented in Table I. The sex distribution of published cases was equal, and the mean age at presentation of intracerebral haemorrhage was 25.4 ± 4.0 years (range, 6–51 years). The mean duration of symptoms before the diagnosis of pheochromocytoma was 2.5 ± 0.7 years (range, 0–7 years), and in our patient it was six months. One patient had haemorrhagic stroke as the presenting feature of pheochromocytoma during preg-

nancy, at the 35th gestational week [7]. Two patients died, and autopsy revealed pheochromocytomas [9, 15]. In this series of patients, six patients had pheochromocytomas (bilateral in two patients, bladder pheochromocytoma in one patient), three patients had paragangliomas (multiple in one patient, malignant in one patient), and one patient had both pheochromocytoma and paragangliomas (Tab. I). Genetic analysis was performed in three patients: one with *SDHD* gene mutation, one with *SDHB* gene mutation (both with paragangliomas), and one patient was negative for screened gene mutations. According to clinical data, a female patient diagnosed during pregnancy had *MEN2A* syndrome, while there were no data for other patients in this series. Our patient had duplication of exon 1 of the *VHL* gene.

The mechanisms that lead to a sudden increase in catecholamine release are varied and not fully understood. There are some widely accepted precipitants, like insufficient/compromised tumour blood supply, direct or indirect physical stimulus to tumour, general anaesthesia, pregnancy, and some drugs [6]. Steroids are described in occasional case reports as a precipitant of pheochromocytoma crisis [22]. Our patient was treated with prednisone four months before intracranial haemorrhage due to hypertensive crisis, and it is possible that prednisone precipitated a surge in catecholamine release.

Management of patients with pheochromocytoma crisis should include haemodynamic stabilisation before surgery. The only indication for emergency surgery without medical stabilisation for crisis patients is shock due to haemorrhagic necrosis or rupture of a pheochromocytoma, with progressive multiorgan failure. Crisis patients who have undergone emergency surgery without medical stabilisation have more intraoperative and postoperative complications and have higher mortality, compared with patients who have undergone elective surgery [23]. Our patient had severe pheochromocytoma crisis, with frequent paroxysms of hypertension, which were difficult to treat. He required high doses of α -blockers in combination with other medications for four months, before haemodynamic stabilisation was achieved, and adrenalectomy was performed without complications during the surgery.

It is currently accepted that up to 35% of pheochromocytoma/paraganglioma are associated with inherited gene mutations [24–29]. Almost one fourth of patients with apparently sporadic pheochromocytoma (non-syndromic pheochromocytoma without a family history of the disease) are carriers of mutations [24]. Younger age, multifocal tumours, and extra-adrenal tumours are significantly associated with the presence of a mutation. Our patient was young and presented dramatically with intracerebral haemorrhage. He was screened for germline mutations of genes associated with familial pheochromocytoma/paragangliomas, and MLPA analysis revealed a duplication of exon 1 of the *VHL* gene. Our patient had only pheochromocytoma without other classical lesions of *VHL* disease and was classified as *VHL* type 2C. His pathohistological finding of vascular invasion and atypical mitosis raised the possibility of tumour recurrence. After two years of follow-up, the patient was still disease-free. It is necessary to maintain lifelong clinical follow-up of the patient by both laboratory and radiological investigation in addition to following the patient's symptoms.

Conclusions

We report a young adult patient with pheochromocytoma presenting with intracerebral haemorrhage caused by severe hypertension, possibly with prednisone as a precipitant of a sudden increase in catecholamine release. Physicians evaluating children and young adults with intracerebral haemorrhage, particularly if hypertension is present, should consider the possibility of catecholamine-secreting tumours. Close collaboration between endocrinologists, anaesthetists, and endocrine surgeons is needed in these difficult cases of pheochromocytoma crisis.

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