Ischemic stroke and hypertension in a child — a case report of two patients

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Abstract

Ischemic stroke is a rare condition in children and is typically a complication of systemic diseases, such as congenital or acquired arterial diseases. The article discusses cases of two patients: a 2.5-year-old girl and a 3.5-year-old boy with ischemic stroke, severe hypertension and with multiple medium-caliber arterial stenosis involving the intracranial segments of the carotid arteries and renal arteries stenoses. Medical imaging showed a developed collateral circulation in the central nervous system typical of moyamoya disease. Molecular confirmation of the RNF213 gene variant was obtained in one patient. Complex drug treatment managed to achieve normotension. In further observation, the development of stenosis in medium-caliber arteries, including the pulmonary vascular bed, was observed. Presented cases show the evolution of vascular alterations in a patient with molecularly confirmed moyamoya disease and in a patient with a similar clinical phenotype without molecular confirmation.

Key words: hypertension; moyamoya disease; ischemic stroke

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Introduction

In adults, ischemic stroke is generally a complication of a long-term cardiovascular disease on the background of atherosclerosis and/or arterial hypertension (HT) [1]. Undiagnosed and untreated heart defects that cause arterial embolism are also a significant cause. In children, ischemic stroke is a rare condition and is generally a complication of congenital or acquired cardiovascular pathologies, particularly of the left atrium, left ventricle, including the interventricular septum, interatrial septum, and arterial bed (Tab. 1) [2, 3]. Congenital or acquired arterial diseases can present with severe HT. This may allow early diagnosis of vascular pathologies and their causal treatment. In children < 16 years of age, blood pressure (BP) should be assessed using percentile grids. In this age group, HT is diagnosed when systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) reach ≥ 95th percentile (cc) for age, gender, and height in 3 independent measurements. In patients ≥ 16 years old HT is diagnosed according to adult criteria — i.e., when SBP and/or DBP reach ≥ 140/90 mm Hg [4]. In school-aged children and adolescents, the predominant form of HT is primary HT, including obesity-related hypertension. In younger children, the predominant form is secondary HT. Secondary HT should also be suspected, regardless of age, in any case of grade 2 or higher HT and/or when there are characteristic laboratory abnormalities and/or significant hypertension mediated organ damage

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Table 1. Overview of the most common causes of ischemic stroke

Most common causes of ischemic stroke		
Underaged [2, 3]		Adults (18 years and older) [68–70]
Infants (1 month)	Older children (1 month–18 years)	
Idiopathic, non-specific	Vascular pathologies (e.g.. moyamoya disease)	Complication of hypertension
Prothrombotic coagulopathies (e.g., thrombophilias)	Prothrombotic coagulopathies (e.g., thrombophilias)	Cardiovascular diseases (e.g., arterial dissections, narrowing of the lumen of vessels in atherosclerosis)
Congenital heart defects and other cardiac pathologies (e.g., ventricular septal defect)	Congenital heart defects and other cardiac pathologies (e.g., ventricular septal defect)	Heart defects and other cardiac pathologies (such as atrial fibrillation)
Infectious (e.g., sepsis)	Head or neck injuries	Prothrombotic coagulopathies (e.g., hyperhomocysteinemia)
Asphyxia	Idiopathic, non-specific	Migraine
Head or neck injuries	Infectious (e.g., meningitis)	Other systemic diseases (e.g., diabetes)

Table 2. Selected causes of secondary hypertension in childhood

Selected causes of secondary hypertension in childhood [4]	
Kidney diseases (e.g., glomerulonephritis)	Induced by drugs and chemical agents, electrolyte disorders (e.g., MAO inhibitors)
Endocrine diseases (e.g., primary hyperaldosteronism)	Gestational hypertension (e.g., preeclampsia)
Cardiovascular diseases (e.g., coarctation of the aorta, aortic regurgitation, middle-aortic syndrome)	Decreased vascular resistance (e.g., arteriovenous fistulas)
Hematological diseases (e.g., anemia)	Hypervolemia (e.g., renal failure)
Neurological diseases (e.g., porphyria)	Obstructive sleep apnea (e.g., obesity)
Cancers (e.g., Wilms' tumor)	Syndromic hypertension (e.g., syndromes: Turner, Marfan, Klinefelter, Down)
Acute stress (e.g., burns)	Monogenic hypertension (e.g., Liddle syndrome)

MAO — monoamine oxidase

(HMOD). The causes of secondary HT in children are shown in Table 2. The purpose of this paper is to describe the cases of children with severe HT and ischemic strokes: a 2.5-year-old girl with recurrent central nervous system (CNS) ischemic strokes and generalized arterial pathology, and a 3.5-year-old boy with a history of CNS ischemic stroke, hypertensive crisis, generalized arterial pathology and pulmonary HT.

Case I

A 2.5-year-old girl was urgently admitted to a hospital in the place of residence because of right-sided limb paresis and central facial nerve paralysis. At that time, blood pressure measurements indicated HT (157/68 mm Hg). Computed tomography (CT) and magnetic resonance imaging (MRI) examinations showed older and new ischemic lesions in CNS. Echocardiography revealed an abnormal left ventricular structure with features of noncompaction and hypertrophy — left ventricular mass index (LVMi) was 65.1 g/m^{2,7} (> 99 cc). Treatment with phenobarbital and valproic acid was implemented due to a seizure episode. According to the mother, the girl developed normally in the first year of life. She has three healthy brothers. Due to uncontrolled, severe hypertension patient was referred to the Department of Nephrology, Kidney Transplantation and Hypertension at the Children`s Memorial Health Institute.

On admission, the girl had persistent right-sided limb paresis. BP reached values up to 151/75 mm Hg, heart rate was 110/min. On physical examination there was a 3/6 Levine systolic murmur radiating to the intercostal region and an abdominal systolic murmur. In the laboratory tests, kidney function markers were abnormal [serum creatinine 0.7 mg/dl, eGFR based on creatinine 53.1 mL/min/1.73 m^2, cystatin C 1.09 mg/l, estimated glomerular filtration rate (eGFR) based on cystatin C 65.2 mL/min/1.73 m^2, urea 81.3 mg/dL] and N-terminal pro-brain natriuretic peptide (NT-proBNP) was elevated (535.5 pg/mL) (Tab. 3). Inflammation markers were normal.

Table 3. Laboratory results of the first patient on admission

Parameter (norm)	Value
Creatinine [mg/dL] N: 0.38–0.54	0.7
eGFR from creatinine [mL/min/1.73 m²] N: < 90	53.1
Cystatin C [mg/L] N: 0.62–1.11	1.09
eGFR form cystatin C [mL/min/1.73 m²] N: < 90	65.2
NTproBNP [pg/mL] N: < 320	535.5
Uric acid [mg/dL] N: 1.8–4.9	4.4
Phosphates [mmol/l] N: 1.38–2.19	1.73
Urine protein [mg/dl] N: 0–15	13
Magnesium [mmol/l] N: 0.7–1.05	0.93
Urea [mg/dL] N: 15.6–45	81.3
Urinalysis	**Value**
Color	Bright yellow
Clarity	Clear
Specific gravity (SG) N: 1.012–1.025	1.005
pH N: 5–7.5	7.0
Protein	Negative
Glucose	Positive
Ketones [mg/dL] N: 0–10	Negative
Bilirubin	Negative
Urobilinogen [mg/dL] N: 0–2	Norm
Leukocytes	Positive
Nitrite	Negative
Blood	Negative
Venous blood gas (VBG)	**Value**
pH N: 7.35–7.43	7.38
pCO2 [mm Hg] N: 45-50	36.6
pO2 [mm Hg] N: 33-53	43.7
HCO_3 current [mmol/L] N: 24–30	21.4
BE [mmol/L] N: –3–2	–3.2
$ctCO_2$ [mmol/L] N: 23-27	22.2
SO_2 (%) N: 54.4–69.2	74.3

eGFR — estimated glomerular filtration rate; NTproBNP — N-terminal pro-brain natriuretic peptide; pCO_2 — partial pressure of carbon dioxide; PO_2 — partial pressure of oxygen; HCO_3 — bicarbonate; BE — blood base excess; $ctCO_2$ — total carbon dioxide concentration in plasma; SO_2 — sulfur dioxide

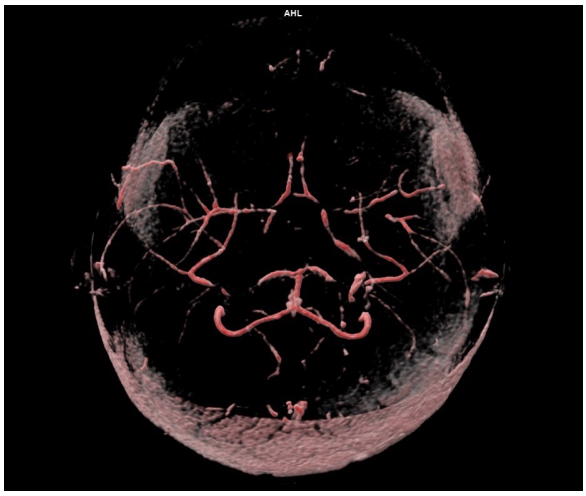

Figure 1. Visible stenosis in the vessels of the circle of Willis, bilateral posterior communicating arteries not visible [magnetic resonance imaging (MRI) reconstruction]

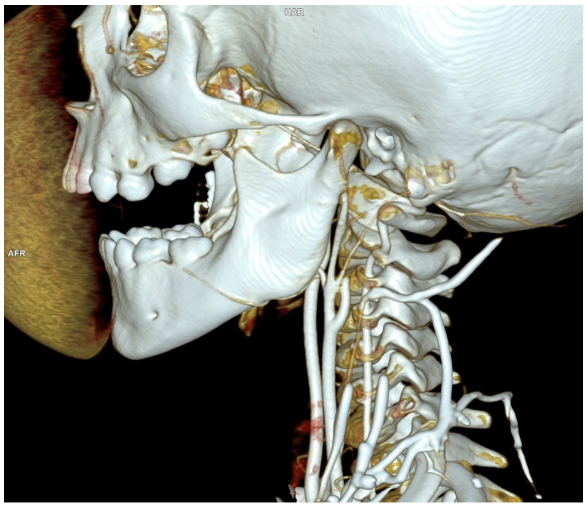

Figure 2. Apparent significant stenosis (amputation) of the left internal carotid artery [magnetic resonance imaging (MRI) reconstruction]

Magnetic resonance angiography (MRA) showed narrowed cerebral and internal carotid arteries and collateral circulation vessels typical of moyamoya disease (Fig. 1, 2). The FLAIR sequence showed extensive hyperintense lesions in the cortex and subcortical white matter of the left hemisphere, as well as numerous small ischemic foci. In addition, volume reduction and asymmetry of the cerebral hemispheres were found. Doppler ultrasonography (USG) showed a reduced size of the right kidney (55 mm, < 1st cc), which was 1 cm smaller than the left kidney (65 mm, 15th cc). The resistance index (RI) in the lower segments of the right kidney was increased (RI = 0.75), while the upper pole of

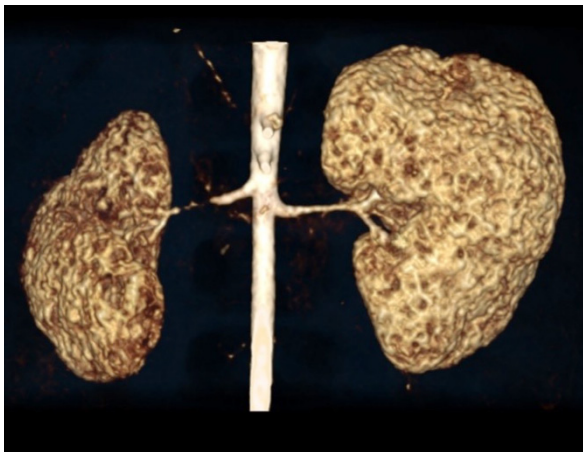

Figure 3. Visible stenosis of the right renal a., left renal a., and superior mesenteric a [computed tomography (CT) angiography reconstruction)

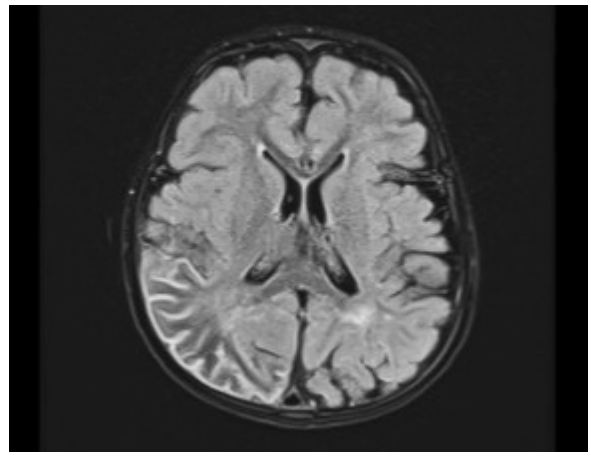

Figure 4. Image consistent with ischemic lesions of the right parietal-occipital cortex [magnetic resonance imaging (MRI)]

the right kidney had a flow with normal resistance (RI = 0.67) but prolonged acceleration time (ACT) (0.2 s). Renal scintigraphy with ethinylecysteamine showed reduced size, impaired secretory function, and tracer retention in the parenchyma of the right kidney and a prolonged third phase in the left kidney. The right kidney's contribution to clearance, assessed as effective renal plasma flow (ERPF%), was 29%. CT scan showed diffuse narrowing of arterial vessels with focal stenoses of the right renal artery and its renal branches, as well as a narrowed left renal artery, superior mesenteric artery, and narrow visceral trunk outlet (Fig. 3).

Due to the distal and possibly intrarenal location of the right renal artery lesion, the patient was disqualified from invasive treatment (surgical or endovascular). The presence of a developed collateral circulation and stenosis of the intracranial segments of the carotid arteries allowed the patient to qualify for a multi-burr hole encephalo-duro-periosteal synangiosis which proceeded without complications. Due to the lack of BP control (BP values reached 190/70 mm Hg) and no possibility of kidney revascularization, antihypertensive treatment was intensified, and a decision was made to administer low doses of an angiotensin convertase inhibitor. Ultimately, the patient required 6 antihypertensive medications: amlodipine, nebivolol, ramipril, spironolactone, hydrochlorothiazide, doxazosin. In addition, the patient received prophylactic doses of anticoagulants. Due to abnormal kidney function (serum creatinine 0.63 mg/dL, eGFR 61 mL/min/1.73 m^2, cystatin C 1.24 mg/dL, eGFR 58 mL/min/1.73 m^2, urea 68 mg/dL), ramipril was discontinued after 2 months. Because of the high risk of CNS ischemia, BP was lowered gradually. After four months, the girl was hospitalized again with another ischemic stroke, which was a complication of Sars-CoV-2 infection, despite anticoagulant treatment (Fig. 4). On admission, BP values reached 180/93 mm Hg. Laboratory markers of kidney function were normal. Based on the clinical picture and laboratory results, antihypertensive treatment was modified — nebivolol was changed to propranolol, the dose of doxazosin was increased and enalapril was added. After six months, follow-up examinations revealed deterioration of kidney function (creatinine 1.28 mg/dL, cystatin C 2.42 mg/dL, urea 83.1 mg/dL), anemization [hemoglobin (Hb) 6 g/dL, hematocrit (Ht) 18%], hyperkalemia (6.78 mmol/L) and metabolic acidosis [bicarbonate (HCO3) 14.1 mmol/L, pH 7.21). Because of that enalapril and spironolactone were discontinued, while due to suspected gastrointestinal bleeding, enoxaparin was discontinued and omeprazole was administered, achieving an improvement in red blood cell parameters. After eight months, the girl was hospitalized again due to high systolic BP values (160 mm Hg). Due to ineffective antihypertensive therapy and contraindications to surgical or intravascular revascularization, it was decided to perform a pharmacological nephrectomy by administering full doses of angiotensin-converting enzyme inhibitor (ACE; enalapril) along with an angiotensin receptor blocker (losartan). A reduction in BP values to 125/52 mm Hg was achieved. As kidney function deteriorated (creatinine 2.73 mg/dL, eGFR 15.1 mL/min/1.73 m^2, cystatin C 2.57 mg/dL, eGFR 29 mL/min/1.73 m^2, urea 170 mg/dL), hemodialysis was started, followed by peritoneal dialysis. The process of qualifying the patient to be put on the waiting list for kidney

transplantation has been started. After nine months, good BP control (110/50 mm Hg) is maintained, left ventricular mass expressed as LVMi on ECHO is 51.7 g/m^{2,7} and the left ventricle has preserved systolic function. Episodes of ischemic strokes/transient ischemic attacks have decreased, and the patient has preserved residual diuresis.

Case II

A 3.5-year-old boy with severe hypertension, with hypertensive crisis in medical history and ischemic stroke, was admitted to the Department of Nephrology, Kidney Transplantation and Hypertension, Children`s Memorial Health Institute in February 2016 for further diagnosis. There were no kidney and urinary tract diseases and cardiovascular diseases in boy's family medical record. Previously, patient had been hospitalized several times due to balance disorders, lower limbs muscle weakness that made walking impossible and very high blood pressure values (220/145 mm Hg). Medical imaging, during diagnosis in the place of residence, revealed ischemic foci in the upper parts of the left frontal lobe. Hypertensive encephalopathy with cerebro-pyramidal syndrome and limbs paresis were diagnosed. There were no other signs of HMOD. Doppler USG suggested left renal artery stenosis. Abdominal angio-CT showed bilaterally accessory renal arteries with suspected stenosis within the left main renal artery. In addition, changes of an ischemic or scarring nature within the renal cortex were described. CNS MRI showed several ischemic foci in the left cerebral hemisphere, hypoplastic left middle and anterior cerebral arteries, bilateral intracranial stenosis of the internal carotid arteries and a diffuse network of collateral circulation. Cerebral bioelectrical activity and EEG results were normal. Before admission to the Department patient's pharmacological treatment consisted of carvedilol, amlodipine, clonidine, enalapril and acetylsalicylic acid. Due to deteriorating kidney function and hyperkalemia, an ACEI was discontinued in following days. Blood pressure values remained in the range of 102–137/56–70 mm Hg. At admission the patient was in good general condition and presented discrete balance disorders and muscle weakness on the left side. Additionally, features of hypertrophy of pharyngeal and palatine tonsils, enlarged lymph nodes of the neck were also evident. Angio-CT images of the abdomen and MRI of the CNS showed vascular abnormalities characteristic for moyamoya disease. In addition to stenosis of both main and accessory renal arteries (bifocal on the right side), stenosis of the abdominal aorta over a long segment, and stenosis of the iliac arteries were found. Within the iliac vessels, an abnormal thickened wall was visualized. Dynamic renal scintigraphy showed marked asymmetry in kidney size — the left kidney was smaller, with impaired secretory function (ERPF% of the left kidney 43%, of the right kidney 57%). Table 4 shows the patient's laboratory results at admission.

During interdisciplinary consultation, it was determined, that for now, vascular intervention was not possible. The patient was qualified for CNS revascularization during multi-burr hole encephalo-duro-periosteal synangiosis as well as simultaneous adenotomy and tonsillectomy. Procedures were performed without complications. The boy required modification of antihypertensive treatment — doxazosin, spironolactone and indapamide were added. Satisfactory control of blood pressure was achieved. Due to the risk of recurrent ischemic stroke, it was intended to maintain a systolic blood pressure (SBP) of 115–135 mm Hg.

At one of the follow-up visits, 7 months later, MRA of the CNS showed malar cavities at the site of previously visible small stroke lesions. Penetration of small extracranial vessels into the neural tissue was found. A date has been set for the next stage of multi-burr hole encephalo-duro-periosteal synangiosis. In addition, the patient underwent angio-CT of the abdominal vessels, which showed double vascularization of the right kidney and right renal arteries without visible stenosis. The left renal artery stenosis was found to be about 1 mm over a length of approximately 5 mm. Distally to the stenosis, the lumen of the renal artery was 2.5 mm in diameter. In addition, asymmetry of kidney size was confirmed - the left kidney was smaller (68 mm — 4th cc) relative to the right kidney (81 mm —74th cc). Stenosis near the bifurcation of the right common iliac artery and the initial segment of the right internal iliac artery was also found. A follow-up dynamic renal scintigraphy was performed, which again confirmed that the left kidney was significantly smaller than the right, with impaired secretory function and efficient excretory function. In the imaging tests, secretory and excretory function of the right kidney were (ERPF%): left kidney 33% right kidney 67%. Office BP values were in the range of the 1st degree hypertension. Additional examinations showed presence of subclinical hypertensive arterial injury [carotid intima-media thickness (cIMT) 0.65mm]. Antihypertensive treatment was modified by increasing doses of doxazosin and spironolactone and angioplasty of

Table 4. Laboratory results on admission of the second patient

Parameter (norm)	Value
Creatinine [mg/dl] N: 0.38–0.54	0.34
Cystatin C [mg/L] N: 0.62–1.11	0.97
Uric acid [mg/dl] N: 1.8–4.9	4.4
Phosphates [mmol/L] N: 1.38–2.19	6.2
Magnesium [mmol/L] N: 0.7–1.05	0.69
Urea [mg/dl] N: 15.6–45	30.8
Urinalysis	**Value**
Color	Bright yellow
Transparency	Clear
Specific gravity (SG) N: 1.012–1.025	1.015
pH N: 5–7.5	6.0
Protein	Negative
Glucose	Negative
Ketones [mg/dl] N: 0–10	Negative
Bilirubin	Negative
Urobilinogen [mg/dl] N: 0–2	0.2
Leukocytes	1–2
Nitrites	Negative
Red blood cells	1 every few fields of view
Flat epithelia	singular
Venous blood gas (VBG)	**Value**
pH N: 7.35–7.43	7.346
pCO2 [mmHg] N: 45–50	42.5
pO2 [mmHg] N: 33–53	73.1
HCO_3 akt. [mmol/L] N: 24–30	213.3
BE [mmol/L] N: –3–2	–1.0
Ionogram	Value
Sodium [mmol/L]	140
Potassium [mmol/L]	4.4
Chlorides [mmol/L]	99

pCO_2 — partial pressure of carbon dioxide; PO_2 — partial pressure of oxygen; HCO_3 — bicarbonate; BE — blood base excess

the left renal artery with paclitaxel releasing balloon was performed.

On follow-up ultrasound, arterial flow in both kidneys was highly resistive, no perioperative complications were visualized. Control scintigraphy showed prolonged tracer transit in the parenchyma of the right kidney and a decrease in the relative contribution of the right kidney to clearance (58%) relative to the left kidney (42%), indicating improved function of the left kidney after angioplasty of the left renal artery. The kidney size ratio remained similar — the right kidney stayed larger in relations to the smaller left kidney. The patient's treatment was modified: propranolol was prescribed, which later was changed to nebivolol. Additionally, ramipril and amlodipine were added to the pharmacologic therapy. On this combination of antihypertensive drugs, BP remained in the SBP range of about 115–120 mm Hg. During the same hospitalization, the second part of neurological surgical treatment (multi-burr hole encephalo-duro-periosteal synangiosis) was also performed.

Next follow-up visit showed further deterioration of left renal function, so an abdominal CT angiography was performed. The examination showed aortic stenosis at the level of the renal artery (diameter: 3.9 mm). The diameter of the left renal artery was approximately 1.5 mm. An uneven outline of the vascular lumen within the renal arteries and abdominal aorta was visible. Stenosis of the right internal and external iliac arteries were still visible, as previously described. The angio-CT of the left kidney showed segmental narrowing of the cortical layer. In laboratory tests slightly increased level of cystatin C was observed (1.19 mg/L). Flow in both kidneys was highly resistive: right kidney RI 0.86, V max 90 cm/sec, left kidney RI 0.8; Vmax up to 50 cm/sec. At this stage, the pharmacological treatment consisted of: nebivolol, ramipril, amlodipine, indapamide, spironolactone, acetylsalicylic acid, and allopurinol.

Over the next two months, progression of the disease and deterioration of the boy's general condition were observed. The boy complained of pain in his lower extremities and a feeling of fatigue and shortness of breath during physical activities. Parents did not observe any new stroke lesions. On physical examination, numerous skin petechiae of the tibia drew were observed. A systolic murmur over the heart of 2/6 on the Levine scale persisted. A normal, symmetrical alveolar murmur was heard over the lungs. A systolic murmur was heard over the entire abdominal cavity. A pulse was felt on the arteries available for examination. In laboratory tests: morphology, renal function markers were

normal, and there were no ionic or venous blood gas abnormalities. Echocardiography showed thickened left ventricular myocardium, turbulent flow in the aortic isthmus (gradient 33 mm Hg) and features of increased pulmonary trunk pressure. The boy underwent a diagnostic cardiac catheterization with an attempt to re-dilate the left renal artery. During the same procedure, catheterization and angiography of the pulmonary arteries were performed. Pulmonary hypertension secondary to stenosis in the distal segments of the pulmonary arteries was diagnosed. A scintigraphy showed multiple areas of decreased perfusion in both lungs. In a 6-minute walking test, patient covered 300m, the test was discontinued after 5 min due to fatigue, no desaturation was observed after exercise. Sildenafil was added to the treatment.

Over the course of subsequent months, patient's performance and physical fitness improved. A subsequent echocardiogram showed a slight pulmonary valve regurgitation. Estimated mean pulmonary trunk pressure was 51 mm Hg (previously 35 mm Hg). The dose of sildenafil was increased, with good tolerance by patient. At the next visit, pulmonary artery systolic flow was 63 m/s estimated mean pulmonary artery pressure (mPAP) was 51 mm Hg. In the 6-minute walk test, the boy covered 420 meters and there was no decrease in blood saturation at the peak of the effort, and the saturation was 99%. A scintigraphy showed that the smaller left kidney with impaired secretory function had a significantly prolonged tracer transit time through the parenchyma compared to previous studies and had a 24% clearance rate. The cumulative curve by the end of the dynamic study also worsened compared to previous studies. The right kidney had efficient secretory and excretory function, with small yet noticeable area of prolonged tracer retention in the parenchyma of the lower pole of the right kidney, what was not evident in previous studies. Another angiotomography was performed to further examine the left renal artery stenosis. In the left kidney, the cortical layer narrowed with apparent segmental atrophy. The single left renal artery had a diameter of about 1.5–2 mm, an uneven lumen and stenosis in the region of the renal hilum to about 1–1.2 mm. The right renal arteries (main artery with a diameter of 2.9 mm, accessory artery with a diameter of 1 mm) had no obvious segmental narrowing. In the right kidney, segmental stenosis of the cortical layer was visualized. During subsequent follow-up visits, antihypertensive treatment was modified according to blood pressure measurements.

Molecular testing revealed that the patient is a heterozygous carrier of a novel molecular variant c.12364G>T p. (Asp4122Tyr) in the RNF 213 gene, which, assuming the pathogenic nature of the mutation, may be clinically significant in the context of the proband's phenotype. The analysis ruled out the presence of the variant in both proband's parents, which in all likelihood indicates that the variant arose de novo and may be pathogenic in nature. Currently, 6 years after the diagnosis, the patient is in good general condition. In a recent 6-minute walk test, the boy covered a distance similar to the previous one = 388m, with no significant decrease in post-exercise saturation. Imaging studies showed smaller dimensions of the pulmonary trunk and pulmonary arteries than before. The most recent echocardiogram showed no significant deterioration from previous studies. Kidney function, periodically monitored by laboratory and USG, also remained unchanged. Blood pressure is currently well controlled.

Discussion

Moyamoya disease (MMD) has an unknown etiology. It occurs more often in females [5, 6] and is diagnosed most often in Far Eastern countries [5]. The disease has an estimated incidence of 10.5/100,000 people in Japan [7] and 16.1/100,000 in South Korea [6]. MMD is associated with variants of RNF213 gene. In contrast the term moyamoya syndrome (MMS) is used in case of typical vascular abnormalities as in MMD but not associated with RNF213 variants. Despite the low incidence of the disease, 10 patients with symptoms characteristic of MMD/MMS were referred to our Department in the past 10 years. MMD leads to narrowing of the cerebral and carotid arteries with the formation of a fine circulatory network of vessels, resembling puff-of smoke (moyamoya in Japanese) in angiography [8, 9]. In addition to stenosis of the head and neck vessels, MMD can cause stenosis of the renal and/or pulmonary arteries and visceral arteries, and lead to the development of renal HT and pulmonary HT [10–12]. Visceral artery stenosis can cause intestinal ischemia and abdominal angina symptoms. In some patients, the disease can be progressive and involve new arterial areas. MMD/MMS is usually diagnosed at two age peaks — around age 5 and 40 [13]. In childhood, ischemic strokes predominate, while in adults, intracranial hemorrhages are caused by rupture of aneurysms of small intracerebral arterioles that develop as the disease progresses

Table 5. Disease type manifested at the initial attack [9]

Disease type	Incidence (%)
TIA	37
Frequent TIA	7
Cerebral infarction	17
Intracerebral hemorrhage	19
Headache	6
Epilepsy	3
Asymptomatic	3
Other	1
Details unknown	17

TIA — transient ischemic attack

[9]. Other symptoms of MMD are shown in Table 5 [9]. There are known case reports of patients who developed progressive pulmonary HT in the course of MMD [12, 14–17]. Histopathological examination of the arteries reveals fibrocellular intimal thickening, an irregular undulation of the internal elastic membrane, and attenuation of the tunica media [13, 18–20].

Moyamoya syndrome (MMS) is a separate clinical phenomenon. It is defined as presence of the characteristic vascular changes described above, with the coexistence of a well-diagnosed systemic disorder or other disease that may have caused such changes [21, 22]. In addition, in MMS, lesions are more likely to occur unilaterally in brain vessels. However, it is necessary for stenoses to involve the anterior circulation to propose a diagnosis of MMS [21]. Characteristic vascular abnormalities in MMD and MMS are sometimes described as moyamoya angiopathy (MMA) [23]. In a Japanese study the most common conditions associated with MMS were: arthrosclerosis (29%), Down syndrome (15.1%), neurofibromatosis type 1 (14%), hyperthyroidism (7.5%), leukemia (2.2%), renal hypertension (2.2%), coarctation of the aorta (2.2%), and meningitis (2.2%) [24]. In contrast, studies from the US reported: sickle cell disease (4. 4%), Down syndrome (4.4%), and neurofibromatosis (2.3%) [25]. Cases of MMS associated with infections or autoimmune diseases have also been described, including bacterial meningitis [22], viral infection (including SARS-CoV-2) [26], and Graves-Basedow disease [27]. SARS-CoV-2 infection may increase morbidity and mortality by exacerbating the symptoms of MMA [28]. Brain tumors and exposure to CNS radiation were documented to be associated with the development of MMS [24, 29, 30]. The course of the MMD and MMS can vary. Feghali et al. reported that MMS patients were younger and less likely to be female; complications of direct or indirect bypass surgeries were more common in MMD than in MMS (33%, 16%, respectively); stroke-free survival time after diagnosis was similar in both groups (3.7 strokes per 100 patients in MMD and 3.5/100 in MMS); MMD patients were more likely to undergo revascularization surgery compared to MMS patients (62% *vs.* 44%) [25]. On the other hand, a 2023 paper comparing patients with MMD with patients with atherosclerosis-associated moyamoya vasculopathy (AS-MMV), reports that over a 4–6-year follow-up period, patients with MMD were more likely to present cerebrovascular events than patients with AS-MMV [31]. The pathophysiology of both MMD and MMS is complex and includes various genetic, inflammatory, and other environmental components [32–34]. Currie et al. in a 2011 paper indicates how specific comorbidities can lead to vascular lumen narrowing in the MMS, e.g., in sickle cell disease, deoxygenated, deformed erythrocytes, containing hemoglobin S, polymerize and show abnormally high adherence to the vessel walls causing vessel lumen narrowing. They also suggest that the high incidence of vascular dysplasia and vascular disease in patients with Down's syndrome increases the chance of diseases involving narrowing of the vascular lumen (including MMS) [22].

For a long time, MMD was considered a non-inflammatory disease, but Masuda et al. described the presence of macrophages and T lymphocytes in vascular areas with smooth muscle cell proliferation, suggesting the influence of inflammatory processes on the formation of arterial occlusion in MMA [35]. The inflammatory response causes proliferation of endothelial cells and hypertrophy of smooth muscle cells, leading to narrowing of the blood vessel lumen. Two possible pathways affecting the development of MMD have been postulated: the anti-inflammatory cytokine pathway and the pro-inflammatory cytokine pathway, which activates the RNF213 protein. The immune response associated with angiogenesis is promoted by M2 macrophages, induced by the anti-inflammatory cytokines: interleukins 4, 10, 13, interferon alpha and transforming growth factor beta [36]. Abnormal expression of other growth factors has also been described in MMD [37–40].

Peng et al. in a 2019 paper reports the results of gene expression profiling (using RNA-seq) in the peripheral blood of MMD patients in comparison to control patients. They obtained 533 differentially expressed genes (DEGs) — specific to MMD. The up-regulated genes were mainly involved in organization of the extracellular matrix (ECM), the development of the CNS or catabolism

of collagen. In contrast, genes with down-regulated expression were responsible for immune and inflammatory response, cellular defense and chemokine-mediated signaling pathway [41]. In the context of MMD, one of the most frequently cited genes encodes the RNF213 protein located on chromosome 17q25.3 [34]. Polymorphic variants of RNF213 4810G>A and 4950G>A have been shown to be significantly more common in patients with MMD than in healthy individuals. Subgroup analyses of the RNF213 polymorphism showed that 4950G>A was more common in patients who suffered from ischemic-type strokes than in patients with hemorrhagic-type strokes. 4810G>A was equally common in both types [42]. The genetic component of MMD can vary significantly depending on the population studied. The c.14576G>A single nucleotide polymorphism, p.R4859K, in RNF-213 was detected in 95% of familial and 79% of sporadic MMD cases. However, some patients with MMD do not carry the c.14576G>A variant, and that percentage is higher in Western countries [42]. Within the Caucasian population, in a study group of 33 patients diagnosed with MMA (including 22 patients with MMD) a significant association between several HLA markers and the occurrence of MMA was found. In all patients in this study group, a significant association was observed between the prevalence of HLA DRB1*03 and HLA-DRB1*13, compared to the control group. In addition, the prevalence of HLA-A*02, HLA-B*08 and HLA-DQB1*03 variants was higher in all patients with MMA and a higher prevalence of HLA-DRB1*03 was observed in 22 patients with MMD, compared to the control group [43]. However, it should be noted that this study was conducted in small group of patients. Studies have also shown the involvement of elevated levels of let-7c microRNAs in pathogenesis of MMD [44]. In a Korean population, the association of the rs11614913 single nucleotide polymorphism in microRNA with MMD has been confirmed [45]. Despite evidence of the association of mutations in certain genes with MMD, the genetic aspect is not the sole and clear determinant of MMD. A case of monozygotic twins has been described in which only one patient developed MMD [46]. Bang et al. in a 2019 paper, suggest that it is necessary to redefine MMD as a spectrum, dependent on multiple factors — including genetic, environmental factors and angiogenetic capacity. They suggest that a broader, better term would be "RNF213 vasculopathies", and that classic MMD may be a subtype manifesting within CNS. The phenotypic variability of MMD and related RNF213 vasculopathies may be due to a complex interaction of the factors mentioned above [34]. Abnormal variants of the RNF213 gene have been shown to be associated not only with MMD, but also with intracranial atherosclerosis and systemic vascular diseases such as pulmonary artery stenosis and renal artery stenosis and may even manifest itself via skin pathologies [34, 47–49]. Studies indicate that the phenotype of diagnosed vasculopathy is also influenced by zygosity for a given mutation [34, 47, 48]. This is important, because heterozygous variants of RNF213 have been found in some of the confirmed cases of MMD, especially those described in Far Eastern countries [50, 51]. Fukushima et al. described two cases of MMD with coexisting pulmonary artery stenosis, in patients with homozygosity for the abnormal variant of RNF1213. Using exome sequencing, both patients were found to have a homozygous c.14429G>A p.Arg4810Lys mutation. Authors suggest that when this mutation occurs in the heterozygous state, it causes classic MMD. In homozygous state, the exact same mutation led to MMD with extracranial systemic vasculopathy manifested in lungs [47]. Similar conclusions are reported by Chang et al. after analyzing the clinical features and genetic analysis of 5 patients and their families [48]. Another case report suggests a novel multi-organ disease from the RNF213 spectrum caused by heterozygous, de novo-derived C-terminal variants in RNF213 [49]. These examples seem to support the claim that mutations within the gene for RNF213 cannot be considered unambiguous confirmation of classic MMD.

The diagnosis of MMD is based on the results of imaging studies such as MRI, angioCT or classic angiography, which can reveal stenosis in the cerebral and carotid arteries and characteristic collateral circulation [9, 13]. Suzuki and Takaku proposed dividing the development of the disease into 6 stages based on angiography (Tab. 6) [8]. 3D images of

Table 6. Course of the Moyamoya disease (MMD) [8]

No.	Stage
1	Narrowing of carotid fork
2	Initiation of the moyamoya
3	Intensification of the moyamoya
4	Minimization of the moyamoya
5	Reduction of the moyamoya
6	Disappearance of the moyamoya

the arterial walls in the CISS (constructive interference in steady state) MRI sequence are of significant diagnostic value [52].

On imaging tests, the appearance of MMD and MMS may differ. MMD is manifested by more concentric thickening, more homogeneous enhancement, larger amount of deep tiny flow voids (DTFVs) and smaller outer-wall boundary area of occlusion compared to atherosclerotic MMS [53]. Characteristic changes in the appearance of vessels in patients with MMD (concentric thickening, constrictive remodeling, and decreased outer diameter) have also been described [52].

MMD treatment should be individualized [54]. Revascularization of intracerebral circulation reduces the risk of ischemic symptoms in patients with MMD. Direct revascularization or indirect bypass surgery are being used [55, 56]. Multi-burr hole encephalo-duro-periosteal synangiosis is an effective method due to the revascularization of a large area of the brain [54]. In addition, antiplatelet drugs may be considered [9].

The presence of HT due to generalized arterial pathology, including renal artery and/or aortic stenosis in patients with MMD is associated with a worse prognosis. Perioperative complications occurred more frequently in patients with HT compared to MMD patients without HT. Lack of antihypertensive treatment was also an independent predictor of more frequent perioperative complications in patients with MMD [57].

In the case of renal artery stenosis, percutaneous intrarenal angioplasty can be performed. In cases of significant distal and intrarenal stenosis, high perioperative risk, and failure of routine antihypertensive therapy, pharmacological nephrectomy may be necessary [58].

The diagnosis of pulmonary hypertension in patients with MMD/MMS is based on X-ray findings, cardiac catheterization, Doppler ECHO findings and scintigraphy [12, 14–17]. If pulmonary hypertension is confirmed, pharmacological treatment can be used. Suggested drugs include sildenafil (which proved effective in our patient), a combination of sildenafil and amlodipine, and bosentan [12, 14, 15, 59].

The emergency mortality rate due to MMD is 2.4% for ischemic strokes and 16.4% for hemorrhagic strokes [60]. Patients whose first symptoms appear at 3–4 years of age have a higher risk of developing mental deterioration and strokes [61]. 89.1% of pediatric patients following multi-burr hole encephalo-duro-periosteal synangiosis did not experience another ischemic stroke or transient ischemic attack (TIA) during a mean follow-up period of 4.2 years [62].

Endovascular interventions in patients with MMD are associated with a higher risk of perioperative complications than in patients from the rest of the population [63, 64]. Among the possible perioperative complications of angioplasty in MMD are vessel rupture/piercing of the patient's artery by microwire and subarachnoid/intracerebral hemorrhage [65, 66]. Ryu et al. in a review of the literature from 2000–2021 reported a risk of perioperative complications among patients with MMD of 9.5%. Authors also noted the high rate of restenosis of operated vessels — 68.8% [66]. Similar percentages were reported by Gross et al. in a 2014 review — perioperative complications occurred in 11% of patients. Restenosis, as assessed by angiography, occurred in 70% of patients [67].

Conclusions

Moyamoya disease is a rare, idiopathic condition leading to narrowing of the cerebral and carotid arteries with the formation of a fine circulatory network of vessels, resembling puff-of smoke in angiography. It is associated with pathological variants of RNF213 gene. Initially, MMD was thought to be a non-inflammatory disease, however, some of the studies indicate the involvement of T lymphocytes and macrophages. Moyamoya syndrome is a clinical condition in which vascular abnormalities typical for MMD are present, however, no RNF213 variants are detected. Pathologies in MMD and MMS are often present in other vessels and both conditions have rather systemic character. The treatment is individualized and includes pharmacological, anti-hypertensive treatment, minimally invasive endovascular interventions, and surgical treatment.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and writing the first draft of the manuscript were performed by J.K. and K.S. M.L., Ł.O. and M.P. edited and reviewed the manuscript critically. All authors read and approved the final manuscript.

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