CASE REPORT

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Unusual case of Parkes-Weber syndrome in a patient with spontaneous subarachnoid hemorrhage

Neobičan slučaj Parkes-Weber-ovog sindroma kod bolesnika sa spontanom subarahnoidnom hemoragijom

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Abstract

Introduction. Parkes-Weber syndrome (PWS) is a complex and rare genetic disease of combined vascular malformations that primarily occur in the extremities and can involve the pelvic blood vessels. In extremely rare cases, the disease is manifested by endocranial and spinal involvement. The treatment of such patients represents a challenge for neurosurgical centers and requires a multidisciplinary approach. **Case report.** We present the case of a 46-year-old male patient admitted to the emergency department due to spontaneous subarachnoid hemorrhage (SAH), moderate flaccid paraparesis, and urinary incontinence. The patient was previously diagnosed with PWS, while the genetic evaluation proved the *RASA1* gene mutation. Furthermore, he experienced a spontaneous SAH and was hospitalized 26 years ago, while six years ago, he underwent a right nephrectomy due to multiple hilar aneurysms of the right renal artery and its branches. Digital subtraction angiography of the endocranium was performed, which detected no aneurysmal dilatations or arteriovenous malformations (AVM). The magnetic resonance imaging recorded spinal intradural AVM in the vertebral levels between T12 and L3, which completely filled the dural sac. After the conservative treatment, there was a significant improvement in the patient's neurological and clinical condition. **Conclusion**. To the best of our knowledge, this is the only case report of a patient with PWS who had a spinal intradural AVM and spontaneous SAH without high-output heart failure and with a history of a previous nephrectomy.

Key words:
arteriovenous malformations; congenital abnormalities; diagnosis; genes; magnetic resonance imaging; mutation; rasa1 protein, human; subarachnoid hemorrhage.

Apstrakt

Uvod. Parkes Weber-ov sindrom (PWS) je kompleksna i retka genetska bolest, koja se manifestuje kombinovanim vaskularnim malformacijama, prvenstveno na krvnim sudovima ekstremiteta, mada mogu biti zahvaćeni i krvni sudovi karlice. Izuzetno retko bolest može imati endokranijalnu i spinalnu lokalizaciju. Lečenje takvih bolesnika predstavlja izazov neurohirurškim centrima i zahteva multidisciplinarni pristup. **Prikaz bolesnika.** Prikazujemo 46-godišnjeg bolesnika, koji je primljen u Urgentni centar zbog spontane subarahnoidne hemoragije (SAH), flakcidne parapareze i urinarne inkontinencije. Bolesniku je prethodno postavljena dijagnoza PWS, a genetskom analizom dokazana je mutacija *RASA1* gena. Takođe, bolesnik je imao SAH i bio hospitalizovan pre 26 godina, dok je pre šest godina, zbog višestrukih hilarnih aneurizmi desne renalne arterije i njenih grana, načinjena desnostrana nefrektomija. Urađena je digitalna subtrakciona angiografija endokranijuma, pri čemu nisu otkrivene aneurizmatske dilatacije i arteriovenske malformacije (AVM). Metodom magnetne rezonance nađena je intraduralna AVM na nivou između pršljenova T12 i L3, koja je u potpunosti ispunila duralnu vreću. Nakon konzervativnog lečenja došlo je do značajnog poboljšanja subjektivnog i kliničkog stanja bolesnika. **Zaključak.** Prema nama dostupnim podacima u referentnoj naučnoj literaturi, ovo je jedini prikaz bolesnika sa PWS sa spinalnom intraduralnom AVM i spontanim SAH bez srčane insuficijencije i sa istorijom prethodne nefrektomije.

Ključne reči:
arteriovenske malformacije; anomalije; dijagnoza; geni; magnetska rezonanca, snimanje; mutacija; rasa1 protein, humani; krvarenje, subarahnoidno.

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Introduction

Parkes-Weber syndrome (PWS) is a complex and rare genetic disease of combined vascular malformations that primarily occur in the extremities and can involve the pelvic blood vessels [1]. Research has shown that the mutation of the *RASA1* gene is responsible for abnormal connections, vascular malformations, and changes in the size of the affected blood vessels. The most common clinical manifestations are "port wine stains" on the skin, venous varicosities, unilateral limb overgrowth, high-flow arteriovenous malformation (AVM), and high-output heart failure [2]. In extremely rare cases, the disease is manifested by endocranial and spinal involvement [3], while the treatment of such patients represents a challenge for neurosurgical centers and requires a multidisciplinary approach. To the best of our knowledge, this is a first reported case of a patient with PWS and spinal AVM who underwent a prior nephrectomy and presented with a perimesencephalic spontaneous subarachnoid hemorrhage (SAH) without intracranial vascular malformation.

Case report

We present a case of a 46-year-old male patient admitted to the emergency department due to severe pain in the lumbar spine with sciatic propagation, as well as sudden headache and neck stiffness. The patient described the headache as the worst in his life.

Furthermore, we obtained relevant medical data from the medical records and heteroanamnesis, evidencing that a patient was previously diagnosed with PWS syndrome, while the genetic evaluation proved the *RASA1* gene mutation. Moreover, the patient's family history of PWS and other vascular malformation syndromes was negative. The patient had previously been under periodical multidisciplinary assessment for the past 30 years. Henceforth, he experienced a spontaneous SAH and was hospitalized 26 years ago, while six years ago, he underwent a right nephrectomy due to multiple hilar aneurysms of the right renal artery and its branches.

During the initial assessment, the patient was drowsy, arterial pressure values were 200/100 mmHg and was rated with a Glasgow Coma Scale score of 14. Neurological examination showed no cranial nerve gross neurological deficits; the neck was stiff, while moderate flaccid paraparesis and urinary incontinence were recorded. An urgent computed tomography (CT) scan of the brain was performed, which revealed spontaneous SAH and intraventricular hemorrhage (IVH) predominantly in the fourth and third cerebral ventricles with a minimal amount of blood in both occipital horns (Figure 1). The Hunt and Hess score was estimated as grade I, the modified World Federation of Neurosurgical Societies grading scale score was evaluated as grade II, while the modified Fisher scale grade was grade IV.

Moreover, a digital subtraction angiography (DSA) of the endocranium was performed, during which no aneurysmal dilatations and AVMs were detected. Magnetic resonance (MR) imaging of the lumbar and thoracic spine was performed, where dilated tortuous intradural blood vessels were present from T12 to L3 vertebral levels, which completely filled the dural sac, measuring 20 × 35 × 90 mm (Figure 2). Above the described AVM, a dilated blood vessel with a diameter of 13 mm was observed up to the recorded level of the C7 vertebral body. That was followed by spinal DSA, which detected the aforementioned AVM feeding from the basin of the tenth intercostal artery on the right side with the formation of numerous small aneurysms and high-flow venous drainage towards the intradural venous plexus. Two dural arteriovenous fistulas were observed at the L2 vertebral level as well (Figures 3 and 4).

On the other hand, an ultrasound of the inguinal region was performed, which recorded an AVM measuring 3 × 1.5 cm in the right inguinal region. Additionally, multiple liver hemangiomas were observed on the abdominal ultrasound examination.

During the hospital treatment, the patient was in an algid stage of the disease, with occasional opisthotonus posture; the pain was controlled with opioid and nonsteroidal analgesics, as well as corticosteroids. Since he exhibited clinical signs of hydrocephalus, a control CT scan of the brain was performed,

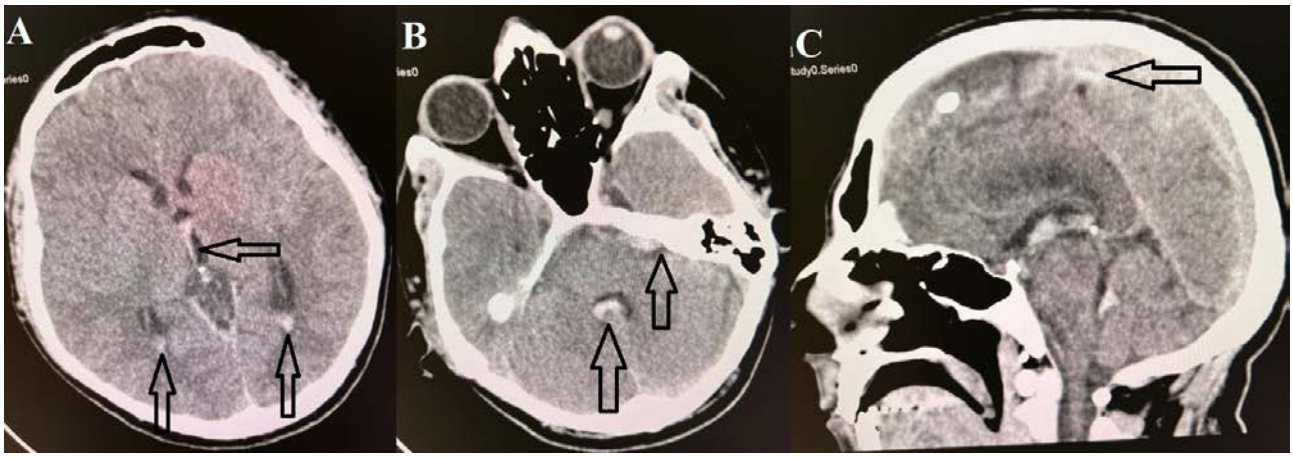

Fig. 1 – Non-contrast axial (A, B) and sagittal (C) tomograms showing subarachnoid hemorrhage recorded in the occipital horns of: A) the lateral and third ventricle, B) fourth ventricle and prepontine cisterns, and C) in the parietal sulci (arrows).

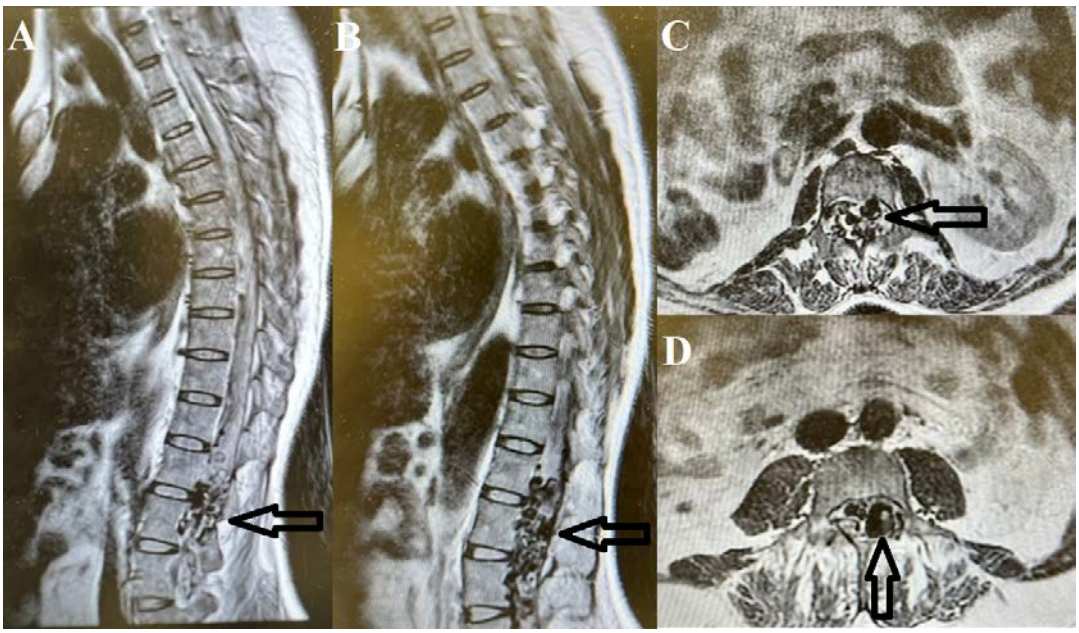

Fig. 2 – Sagittal (A, B) and axial (C, D) magnetic resonance tomograms – at the vertebral levels between T12 and L3, there is a malformation in the spinal canal consisting of numerous tubular and dominantly intradural convoluted flow voids, corresponding to dilated and tortuous blood vessels, measuring 20 × 35 × 90 mm and corresponding to the nidus of arteriovenous malformation (arrows).

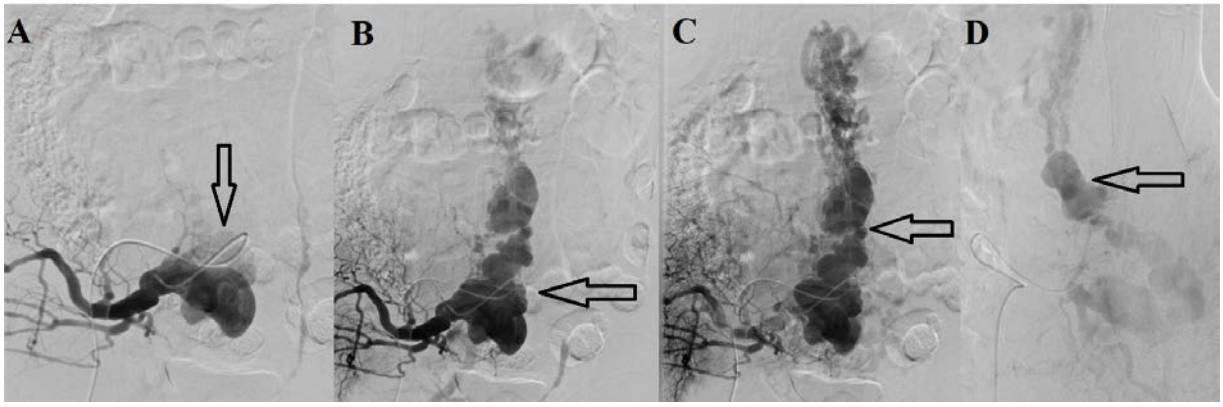

Fig. 3 – Digital subtraction angiography through arterial (A), parenchymal (B, C), and venous (D) phases shows a wide, high-flow arteriovenous fistula (arrows) with rapid venous drainage from the basin of the right internal iliac artery through markedly ectatic and tortuous efferent blood vessels to the spinal venous plexus.

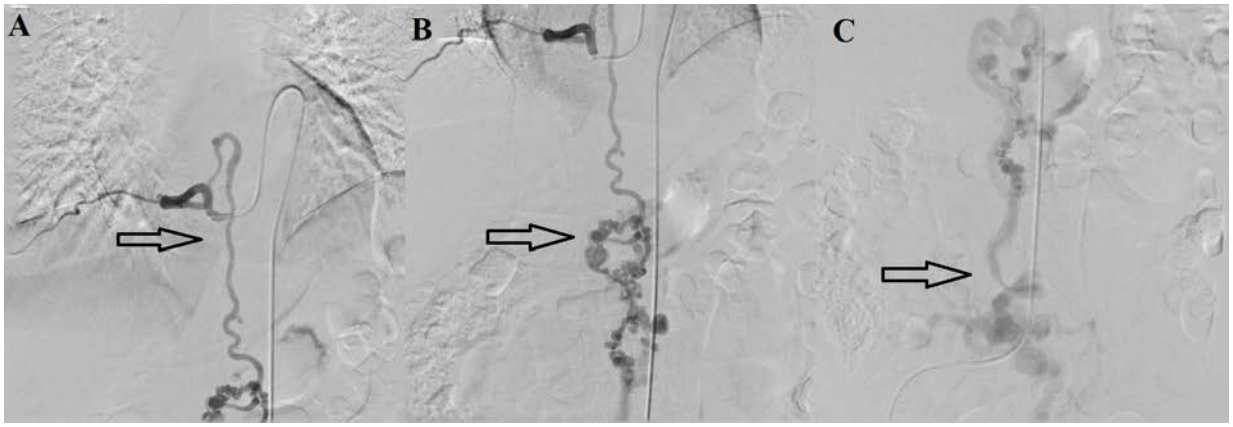

Fig. 4 – Digital subtraction angiograms through arterial (A), parenchymal (B), and venous (C) phases show an extensive arteriovenous malformation (arrows) with a dominant feeder from the basin of the right X intercostal artery, with the formation of numerous smaller aneurysmal dilatations on the afferent branches and with rapid venous drainage through ectatic and extremely tortuous venous plexus.

which indicated the existence of hydrocephalus with periventricular lucency and IVH (Figure 5).

The patient and his family were proposed surgical treatment of hydrocephalus with ventriculoperitoneal shunt or external ventricular drainage, as well as subsequent endovascular treatment of the AVM. However, the patient and his relatives refused further treatment.

Therefore, his hydrocephalus was treated conservatively for seven days with acetazolamide (250 mg a day), furosemide (20 mg twice a day), dexamethasone (8 mg three times a day) with a gradual dose reduction, mannitol (125 mL four times a day) for four days with rehydration and other symptomatic therapy, as well as daily checkup of electrolytes, urea, and creatinine. After the conservative treatment, there was a significant improvement in the patient's subjective and clinical condition, and he was discharged with a recommendation to return for a follow-up CT scan of the brain and further treatment of the AVM. Follow-up examinations were performed after one year and after 18 months, while the patient had paraplegia and urinary incontinence in the clinical presentation and still refused surgical treatment and control radiological diagnostics.

Discussion

PWS is most usually clinically manifested by unilateral limb overgrowth, high-output heart failure, distal arterial ischemia, and venous ulceration, while aneurysms, intracranial and spinal AVM, and malignancies occur less frequently [1, 2]. Based on a review of the available scientific literature, only one previous case of spinal AVM in a patient with PWS has been reported, who suffered from an SAH, while the MR angiography was negative [4]. We believe that the limitation of that case report was the fact that the authors did not perform

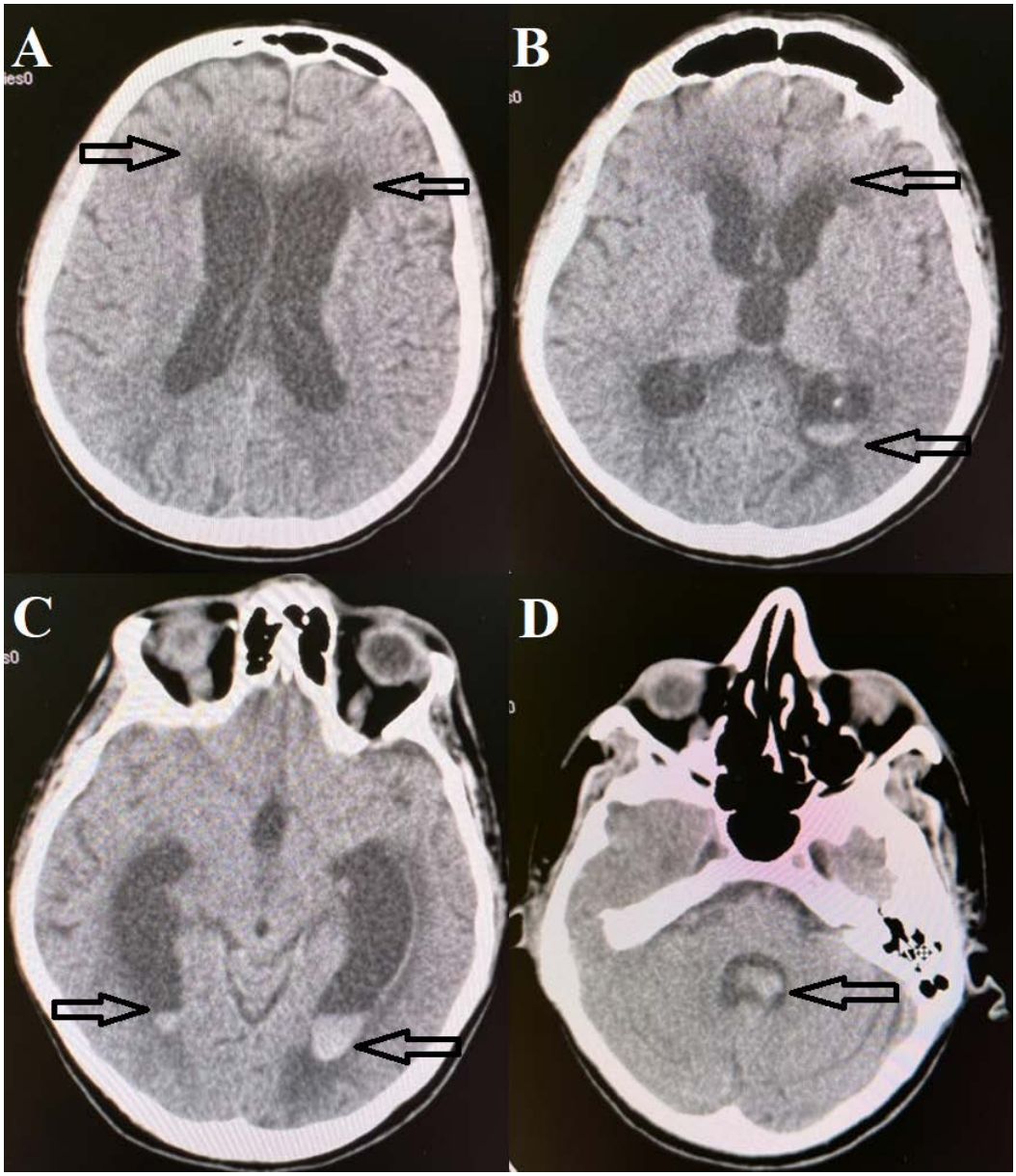

Fig. 5 – Non-contrast axial computed tomography findings indicate the existence of hydrocephalus with periventricular lucency (A, B, C), intraventricular hemorrhage (IVH) in the occipital horns of the lateral ventricles (B, C), and IVH in the fourth (D) ventricle (arrows).

DSA of the brain, which represents the gold standard. Therefore, the existence of a cerebral AVM or aneurysm could not be ruled out with certainty. Furthermore, no genetic evaluation of that patient was performed. In our case, on the other hand, the patient underwent DSA of the brain, and vascular malformations and aneurysms were excluded as potential causes of spontaneous SAH. On the other hand, to the best of our knowledge, this is the only published case of PWS without high-output heart failure, with a history of renal artery aneurysm and subsequent nephrectomy, as well as with intracranial and spinal involvement.

Different studies have shown that predictive parameters for the outcome in patients with SAH are the following: initial neurological status, Fisher score on brain CT, age, history of hypertension, recurrence of SAH, and vasospasm [5, 6]. Some authors suggest that *de novo* hypertension in patients after unilateral nephrectomy can occur due to a reduced total number of nephrons and increased cardiac output, as well as a relative deficiency of 11-beta hydroxylase [7]. Moreover, a clear connection between arterial hypertension and the occurrence of SAH has been previously demonstrated, which is the probable mechanism for the perimesencephalic SAH in our patient [8]. On the other hand, biomarkers that showed prognostic significance in immune dysregulation after SAH, such as C-reactive protein (CRP), interleukins, and neutrophil-lymphocyte ratio, were studied [9, 10]. In cardiovascular diseases, cancer, and sepsis, an elevated neutrophil-lymphocyte ratio has been shown to be a potential indicator of poor clinical outcome [11]. Our patient had verified arterial hypertension after nephrectomy, was middle-aged, and the initial scan showed a modified Fisher score of IV, while his paraparesis was attributed to a spinal AVM instead of SAH. Furthermore, he had relatively low CRP values, low platelet-lymphocyte ratio, and neutrophil-lymphocyte ratio of less than 5. The results of one study showed that a neutrophil-lymphocyte ratio greater than 5.9 predicted as much as a 2-fold greater chance of developing delayed cerebral ischemia after SAH [11]. Although surgical and endovascular treatments were not performed, the patient reached a good recovery, which is in agreement with the aforementioned parameters for predicting the outcome in patients with SAH. Previous studies have shown that angiographically negative SAH, such as perimesencephalic SAH, most often results in good recovery of the patient, and some authors consider it a benign condition because it rarely causes complications such as rebleeding and vasospasm [12]. Moreover, if acute hydrocephalus occurs after a perimesencephalic hemorrhage, it is usually transient and leads to a good recovery of the patient [13], as was the case in our patient.

Surgical treatment of hydrocephalus includes methods such as surgical resolving of the obstruction site, bypassing the obstruction with an alternative route artificially created by endoscopic third ventriculostomy, or by draining cerebrospinal fluid (CSF) from the cerebral ventricles into various absorbent body cavities. Therefore, the CSF drainage procedure can be performed as a ventriculoperitoneal shunt, ventriculoatrial and ventriculopleural shunt, while a lumboperitoneal shunt is rarely used. Various complications can occur after shunt placement surgery, such as obstruction, catheter migration, mechanical blockage, siphoning effect, and infection resulting from colonization of the device by microorganisms [14, 15].

Conservative treatment of hydrocephalus with acetazolamide achieves direct inhibition of carbonic anhydrase in the choroid plexus as well as inhibition of water conductance mediated by aquaporins, which leads to reduced production of CSF. Moreover, for this purpose, acetazolamide is often combined with furosemide. However, the use of corticosteroids in the treatment of hydrocephalus leads to a reduction of inflammation and fibrosis in the subarachnoid compartment. On the other hand, mannitol is occasionally used in the treatment of hydrocephalus in cases of intracranial bleeding [16].

Furthermore, digoxin can be used in the treatment of hydrocephalus, in doses that are not cardiotoxic, as well as urokinase and tissue plasminogen activator, although some previous research indicates that fibrinolytic agents can promote an inflammatory response by rapidly dissolving the clot [16, 17]. Consequently, during the conservative treatment of hydrocephalus in our patient, we opted for the aforementioned therapy, except for digoxin and fibrinolytic agents, because our neurosurgery center lacks experience in their use for this indication.

Surgical treatment of AVM in patients with PWS usually follows unsuccessful conservative treatment and includes amputation of the affected limb, debulking of soft tissues, ligation of AVM feeder, resection of AVM nidus, vein stripping, and epiphyseal stapling for leg length discrepancy. The purpose of treatment is to prevent the occurrence and progression of high-output heart failure, aneurysms, distal ischemia, refractory pain syndrome, ulceration, hemorrhage, and hypertrophy of the affected limb [10, 11]. Moreover, surgical treatment is associated with the occurrence of postoperative complications and has been suppressed, over time, to a significant extent by endovascular procedures [11]. On the other hand, it is impossible to completely cure vascular malformations in PWS due to a tendency for collateral blood vessels to re-appear, as well as for arteriovenous fistulas and AVM relapse as a consequence of the diffuse nature of the disease. That would imply frequent reoperations of the AVM, and for these reasons, embolization is increasingly performed as an initial intervention [10].

The future in the treatment of these patients should be oriented towards targeted molecular therapy, which emphasizes the importance of molecular genetic testing in vascular malformation syndromes. Although there is no official recommendation for targeted molecular therapy for PWS, studies with angiogenesis inhibitors and other agents such as rapamycin, trametinib, thalidomide, and bevacizumab are being conducted to determine their potential efficacy [18].

Considering all this, our findings suggest that this patient was prone to develop intracranial SAH even though he did not have an intracranial vascular malformation as part of PWS, which could be explained by de novo hypertension after unilateral nephrectomy.

Further research comparing the efficiency of different therapeutic modalities for PWS is needed as available data are scarce.

Conclusion

Multidisciplinary assessment and treatment of patients with PWS is necessary due to the complexity of the disease, while their treatment represents a challenge for experienced neurosurgeons and interventional neuroradiologists. To the best of our knowledge, this is the only case report of a patient with PWS who had a spinal AVM and spontaneous perimesencephalic SAH without high-output heart failure and with a history of a previous nephrectomy.

Conflict of interest

The authors declare no conflicts of interest and report no sources of support that require acknowledgment.

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