CASE REPORTS

UDC: 616-056.7-06:[616.831-005+616.831-007.23
DOI: https://doi.org/10.2298/VSP210829022V

Moyamoya syndrome in Schimke immuno-osseous dysplasia

Mojamoja sindrom u Šimkeovoj imuno-osealnoj displaziji

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Abstract

Introduction. Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive multisystem disorder associated with biallelic mutations of the *SMARCAL1* gene. Vascular central nervous system complications in the form of Moyamoya syndrome (MMS) have been reported as a comorbidity in nearly half of the patients clinically presenting with severe migraine-like headaches, transient ischemic attacks (TIA), and ischemic or hemorrhagic infarctions. We present an illustrative case of an infantile form of SIOD with MMS, with a review of the latest diagnostic possibilities, as well as current diagnostic and therapeutic dilemmas in managing SIOD. **Case report.** We present a female patient with the infantile form of SIOD. The proband was born small for gestational age in the 34th gestation week with characteristic dysmorphic features. Genetic testing found a biallelic, nonsense mutation c.2542G>T in the *SMARCAL1* gene. The patient presented early with TIA, seizures, and recurrent ischemic strokes. Magnetic resonance imaging (MRI) confirmed the presence of progressive brain atrophy with bilateral occlusion/stenosis of middle cerebral artery and anterior cerebral artery and a smoke-like collateral vessel appearance consistent with the MMS. At the age of 5 years and 9 months, the patient developed a high fever and cough with unknown cause, with a low erythrocyte and white blood cell count during four weeks, with a poor therapeutic response to antibiotics, transfusion of red blood cells, and granulocyte growth factor. She later died. **Conclusion.** Patients with SIOD may present progressive cerebral vascular changes and clinical neurologic deterioration early in the course of the disease. In such patients, early diagnosis and preventive revascularization surgery are of paramount importance. In diagnosing MMS, MRI angiography can be an appropriate substitute for standard invasive cerebral angiography.

Key words:
cerebrovascular disorders; diagnosis; magnetic resonance imaging; moyamoya disease; mutation; neurologic manifestation.

Apstrakt

Uvod. Šimkeova imuno-osealna displazija (SIOD) je autozomno recesivno multisistemsko oboljenje, povezano sa bialelskim mutacijama gena *SMARCAL1*. Vaskularne komplikacije u centralnom nervnom sistemu u formi Mojamoja sindroma (MMS) javljaju se kao komorbiditet kod gotovo polovine bolesnika, manifestujući se klinički jakim glavoboljama nalik na migrenozne, tranzitornim ishemijskim atacima (TIA) i ishemijskim ili hemoragijskim infarktima. Prikazujemo ilustrativan slučaj infantilnog oblika SIOD sa MMS, sa pregledom najnovijih dijagnostičkih mogućnosti i trenutno najvažnijih dijagnostičko-terapijskih dilema vezanih za SIOD. **Prikaz bolesnika.** Prikazujemo bolesnicu sa infantilnim oblikom SIOD-e, koja je rođena sa težinom manjom od referentne za gestacijsku starost, u 34. gestacijskoj nedelji, sa manifestovanim karakterističnim dismorfizmima. Genetsko testiranje je otkrilo istovetnu *nonsense* mutaciju c.2542G>T na oba alela gena *SMARCAL1*. Bolesnica je imala više epizoda TIA, konvulzija i ishemijskih moždanih udara. Ispitivanja magetskom rezonancom (MRI) pokazala su progresivnu atrofiju mozga sa bilateralnom okluzijom/stenozom srednje i prednje cerebralne arterije i razvoj kolateralnih krvih sudova pod slikom „duvanskog dima" karakteristično za MMS. U uzrastu od 5 godina i 9 meseci, bolesnica je dobila visoku temperaturu i kašalj, nepoznatog uzroka, praćene niskim brojem eritrocita i leukocita tokom 4 nedelje i slabim odgovorom na terapiju antibioticima, transfuziju eritrocita i faktor stimulacije rasta granulocita. Nakon ove epizode

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bolesnica je preminula. **Zaključak.** Oboleli od SIOD-e mogu razviti progresivne promene krvnih sudova mozga i kliničke manifestacije neurološkog propadanja u ranoj fazi bolesti. Kod takvih pacijenata od najvećeg značaja je rano postavljanje dijagnoze i preventivna hirurška revaskularizacija. U dijagnozi MMS, magnetna angiografija može biti adekvatna zamena standardnoj invanzivnoj angiografiji mozga.

Ključne reči:
cerebrovaskularni poremećaji; dijagnoza; Moyamoya bolest; mutacija; magnetska rezonanca, snimanje.

Introduction

Schimke immuno-osseous dysplasia (SIOD) is an autosomal recessive multisystem disorder associated with mutations of the *SMARCAL1* (SWI/SNF2 related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1) gene [1]. *SMARCAL1* encodes a chromatin remodeling enzyme with multiple roles in DNA restructuring [2]. Mutations of this gene are essentially affecting cellular proliferation and differentiation [3, 4]. Disruption of chromatin remodeling is a predisposing factor for nonatherosclerotic occlusive cerebrovascular disease observed in such patients [5]. Vascular central nervous system complications in the form of Moyamoya syndrome (MMS) have been reported as a comorbidity in nearly half of the cases clinically presenting with severe migraine-like headaches, transient ischemic attacks (TIA), and ischemic or hemorrhagic infarctions [3, 6, 7]. Moyamoya disease (MMD) is a rare progressive bilateral stenoocclusive arteriopathy of unknown origin. The disease involves the distal end of both internal carotid arteries and their branches, clinically presenting with recurrent strokes in children [8].

SIOD is hallmarked by growth failure, skeletal dysplasia, steroid-resistant nephrotic syndrome, renal failure, immunodeficiency, and neurologic and pulmonary abnormalities. Patients can be generally divided into two groups – those with a juvenile or early-onset form of SIOD have a much more severe disease course, while patients with later onset have more favorable outcomes, surviving into adulthood [2, 3, 6, 7].

Stajić et al. [9] should be credited with leading the way in managing and treating SIOD patients in Serbia, and, to the best of our knowledge, they described and published the first case of SIOD from Serbia. Boerkoel et al. [10] were the first to show cerebral vascular abnormalities on MRA in two unrelated female SIOD patients. Both patients had cerebral vascular changes, first officially named MMD ("puff of smoke") by Suzuki and Takaku [11] in 1969. As already pointed out, when Moyamoya appears in the form of an isolated condition, it is named MMD, but when it is associated with certain known comorbid genetic conditions, such as SIOD, neurofibromatosis I, sickle cell anemia, or Down syndrome, it is named MMS. In either case, the hallmark of Moyamoya is progressive occlusion of major cerebral arteries [12, 13].

Case report

The presented female patient was born by an emergency Cesarean section in the 34th gestational week, 44 cm long and weighing 1,280 g. Diagnosis of intrauterine growth retardation (IUGR) was made prenatally. She was the firstborn child of healthy, nonconsanguineous Serbian parents. During the first 23 months of life, characteristic dysmorphic features became evident: disproportionate short stature (below the 3rd percentile for age and gender), spondyloepiphyseal dysplasia (flattened vertebral bodies and dysplastic acetabular fossae), a short neck, triangular face, broad nasal tip, sparse and dry hair, multiple hyperpigmented macules, and absent dentition. Growth hormone secretion and thyroid function tests were normal. The immunophenotype of peripheral blood lymphocytes demonstrated a strikingly low number of lymphocytes, particularly of T cells, with a normal CD4/CD8 ratio and a slightly increased number of natural killer (NK) cells. Immunoglobulin levels were normal. Her neurologic development was appropriate for her age. The patient's clinical and laboratory findings suggested the diagnosis of SIOD, which was confirmed by genetic testing demonstrating that she had a biallelic, nonsense mutation c.2542G>T in the *SMARCAL1* gene.

The first neurologic symptoms appeared at the age of 25 months, with a brief transient aphasic episode. The patient's electroencephalogram (EEG) showed a bilateral parietal-occipital slow delta dysfunction, and a diagnosis of TIA was made. Four months later, she had a different type of attack manifested by tremors in the right hand and leg lasting under 5 min, followed by a similar left-sided attack about a month later. Based on a repeated EEG, a diagnosis of partial epilepsy was made, and carbamazepine therapy was initiated.

Her first magnetic resonance imaging (MRI), done when she was 2.5 years old, demonstrated brain atrophy, ischemic leukoencephalopathy, and subcortical laminar cerebral necrosis (Figure 1A). Three-dimensional time of flight (3DTOF) (magnetic resonance angiogram – MRA) showed an absence of flow in the right middle cerebral artery (MCA) (Figure 1B). She had two more aphasic episodes, and after the last one, she was left with a permanent inability to speak at the age of 32 months. Due to her low body weight and poor general condition, she was not accepted for revascularization surgery. Tests for congenital and acquired thrombophilia were negative. Antithrombotic therapy with acetylsalicylic acid (Aspirin®) was initiated after her first MRA; however, since her neurological condition deteriorated, her treatment continued with combined antithrombotic and anticoagulation drugs (Aspirin®, dipyridamole, and warfarin) bearing in mind her international normalized ratio (INR) which had to be kept below 3.

MRI and MRA were repeated 14 months after the first MRI examination, showing more pronounced brain atrophy and bilateral chronic subdural hematomas (Figure 1 C). Cerebral angiography demonstrated bilateral occlusion/stenosis of MCA and anterior cerebral artery (ACA) with collateral

circulation consistent with MMS (Figure 1D). Extracranial vessels ultrasound was not performed, but MRI did show the presence of extracranial collateral circulation. Because of the presence of subdural hematomas, Aspirin® and warfarin were withdrawn, and dipyridamole was continued. She subsequently had several more attacks, usually left-sided. Spastic left-sided weakness gradually developed and remained present on repeated physical examinations. Over time, contractures in her lower extremities affected her everyday activities until her ability to walk was lost completely.

Significant proteinuria was first observed when she was 30 months old (5 months after her first aphasia attack), and hypercholesterolemia was noticed a month later. Our patient never had high blood pressure. The signs of renal failure never appeared, and her urea and creatinine were constantly within normal limits. Chronic anemia developed when she was 5 years old. The white blood cell count (WBC) was within the normal range except during her infrequent acute infections, with the absolute lymphocyte count slightly below the normal range. At the age of 5 years and 9 months, she developed a high fever and cough, with a low erythrocyte and WBC count. The fever with a low WBC count, marked by a very low neutrophil count, continued for the next four weeks. She had a poor therapeutic response to antibiotics, transfusion of red blood cells, and granulocyte growth factor. The cause of the fever was never determined and, during this episode, she died.

Discussion

SIOD is a rare multisystem autosomal recessive disorder. Its prevalence is unknown, but in the United States, it is estimated at between 1 : 1,000,000 and 1 : 3,000,000 [14]. SIOD is mainly characterized by disproportionate short stature

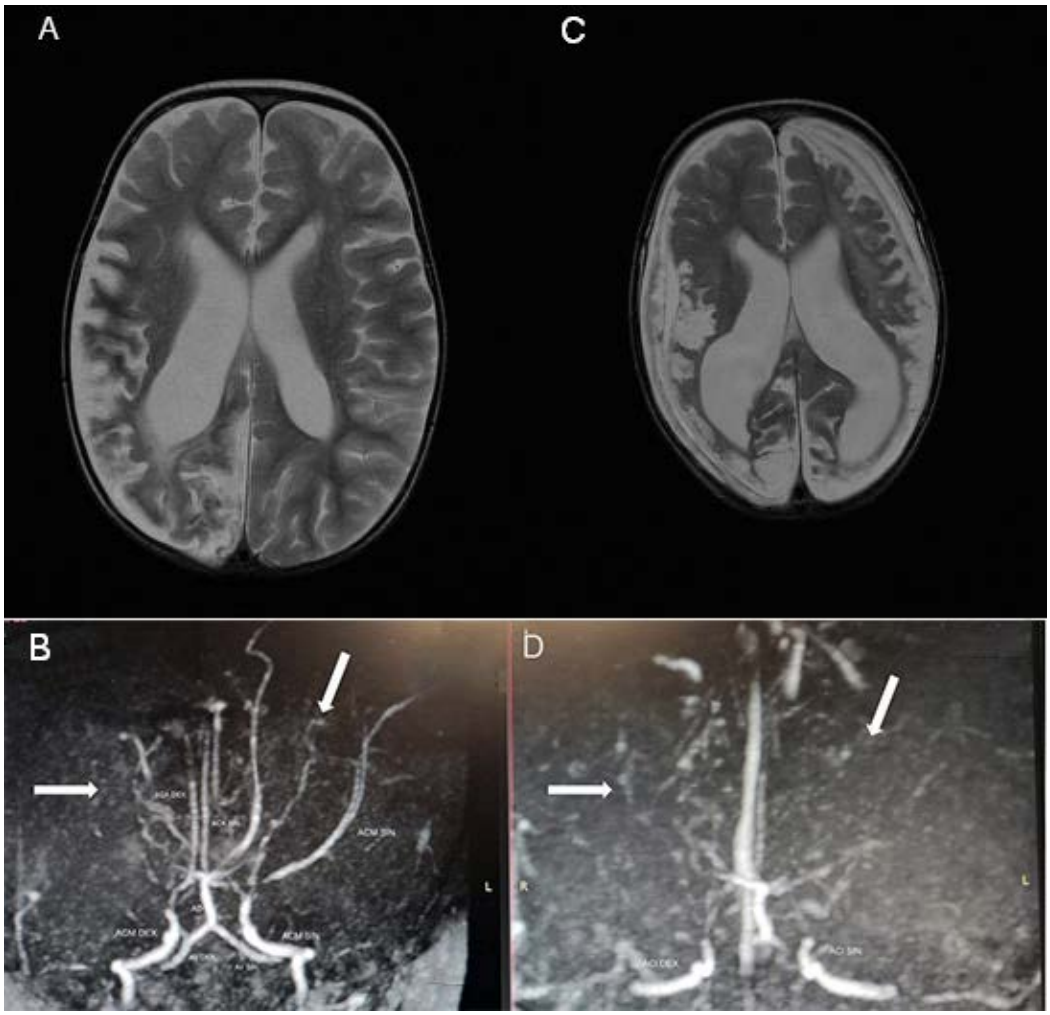

Fig. 1 – A. Right temporal and partial occipital lobe atrophy with increased signal intensity in the cortex, and the dilatation of the ventricular system; B. Absence of contrast flow in the right middle cerebral artery (MCA) with the bilateral abnormal collateral flow and bilateral shadows (arrows) on the same scan level at the basal ganglia region consistent with magnetic resonance imaging Moyamoya stage 2; C. Bilateral chronic subdural hematomas with sediment in the posterior portions of hematomas on the left side and more pronounced both brain atrophy and ventricular dilatation; D. Absent flow in both MCAs and flow reduction in both anterior cerebral arteries with the significantly less prominent collateral flow (arrows) consistent with advanced magnetic resonance imaging Moyamoya stage 3.

due to spondyloepiphyseal dysplasia, T-cell immunodeficiency, and progressive steroid-resistant nephropathy [3, 6, 7]. Although this combination is unique to SIOD, a definitive diagnosis was made only after molecular genetic testing, which confirmed the presence of the biallelic pathogenic mutation in *SMARCAL1* gene. However, there are significant phenotype-to-genotype variations suggesting that SIOD is modified by factors such as environment, epigenetics, and oligogenic inheritance [7]. Moreover, since only 50%–60% of individuals with typical SIOD features have detectable *SMARCAL1* gene mutations, it is proposed that mutations of unidentified genes can also produce the same phenotype [15].

Our patient presented with all the typical characteristics of the infantile form of SIOD. Physical features such as IUGR and short stature are present in 70% and 99% of affected individuals, respectively [7]. Lymphopenia caused by T-cell deficiency, as in the presented case, affects about 80% of SIOD patients and is consistent with reduced production of T cells by the thymus [7, 16]. Absent expression of interleukin 7Rα is blamed for the reduction of the total T cell count [17]. Bertulli et al. [18] recently described a familial SIOD case with defective expression of interleukin 7Rα and alterations of the NK cells. Bone marrow failure occurs in up to one-third of SIOD patients, and it could explain the deficiencies of all blood count lineages observed in our patient at the onset and during her final febrile illness [3, 7]. Infection is the primary cause of death of such patients (23%), while stroke (13%) and renal failure (11%) are less represented [7].

Even though our patient developed steroid-resistant nephrotic syndrome during the course of the disease, signs of renal failure never appeared, and renal disease did not show clinical progression. Treatment attempts with angiotensin-converting enzyme inhibitors and prednisolone were unsuccessful, as described in most publications [7, 14]. Unfortunately, a renal biopsy was never performed, so we could not assess the probable presence and extent of focal glomerular sclerosis.

MMD and MMS is a rare progressive bilateral steno–occlusive arteriopathy clinically presenting with recurrent strokes in children [8]. As stenosis progresses, a compensatory mesh of small collateral vessels develops, presenting on catheter angiography in the form of a cloudy, smoke-like appearance named “moya-moya”, which is the Japanese term for a “puff of smoke”. According to the results from the International Pediatric Stroke Study, approximately one-third to one-half of SIOD has a MMS. Nevertheless, SIOD is a rare cause of MMS, while sickle cell anemia, Down syndrome, and neurofibromatosis I are much more frequent [8].

MMD is responsible for about 8% of arterial strokes in children [8]. Ninety percent of children with MMD had an ischemic stroke, 7.5% presented with TIA, while hemorrhagic stroke was the dominant form of presentation in only 2.5% [8]. Among the children with arterial ischemic stroke, hemiparesis was the most common presenting sign (79%), speech difficulties were observed in 49%, while headache and seizures were reported in 47% and 30%, respectively [8].

TIA was the first mode of presentation in our patient who initially had a brief aphasic episode. Rafay et al. [19] state that in children with MMS, TIA is often associated with hyperventilation suggesting hypoperfusion rather than thrombotic vasoocclusion as a prominent mechanism. Some other authors do not make a clinical distinction between stroke/TIA [9]. After her first aphasia attack, the girl rapidly and completely recovered, suggesting cerebral hypoperfusion as an underlying mechanism.

Nonetheless, within the next 5 months, her neurological status rapidly deteriorated with progressive mental decline, behavioral changes, more profound speech difficulties, and partial epilepsy, clinically strongly suggesting the presence of ischemic strokes. It is not possible to assess the exact time of appearance of infarctions since the first brain MRI done 5 months after the appearance of the neurological symptoms already demonstrated the presence of brain atrophy, ischemic leukoencephalopathy, and subcortical laminar cerebral necrosis (Figure 1A). Such findings are consistent with both fresh and old ischemic strokes. Middle and proximal anterior cerebral arteries (ACA) are known to be the most frequently involved arterial territories affected by ischemic infarctions in pediatric MMD [19]. During the next 14 months, her clinical condition further deteriorated, and repeated MRI showed complete obstruction of both MCA and ACA with a mesh of tiny collateral network confirming the MMS cerebral angiopathy within the SIOD.

The exact mechanism of arterial stenosis in MMD is yet to be fully elucidated. The theory of cerebral atherosclerosis was supported by vascular changes observed on *post-mortem* examinations which showed focal intimal lipid deposits, focal myointimal proliferation, macrophage invasion, foam cells, fibrous transformation, and calcium deposits [7]. Hypertension and hyperlipidemia caused by nephrotic syndrome, present in almost all SIOD patients, were also believed to accentuate thromboembolic atherosclerosis with the progression of arterial stenosis [20]. However, more than 15 years ago, it was demonstrated that successful renal transplantation in SIOD does not stop the progression of cerebral vascular stenosis, suggesting that renal disease alone is not the main reason for the progression of cerebral angiopathy [14, 17].

Efforts should be made in early diagnosing such subgroups of patients in order to enable them for early preventive revascularization surgery [9].

Antiplatelet agents are recommended in Japanese 2012 guidelines for the treatment of ischemic MMD [13]. The J-ASPECT study demonstrated that prehospital use of Aspirin® in patients with ischemic MMD in Japan was associated with a better functional status on hospital admission [21]. The combination of two antiplatelet drugs (Aspirin® and dipyridamole as the most common) seems to be more effective than a single antiplatelet drug in preventing early stroke recurrence [22].

Most pediatric MMD patients were treated with Aspirin® alone, but 20–50% were on anticoagulation therapy [8, 19]. Initially, our patient was treated with Aspirin® alone. As the neurological disease progressed, dipyridamole was added, but it did not affect the appearance of her recurrent ischemic attacks. She was refused revascularization surgery due to her low body weight and poor general condition. Since there were no other treatment options, off label use of combined antiplatelet and

anticoagulation therapy was attempted bearing in mind to keep her INR below 3. That was based on adult data which suggested that adding warfarin to Aspirin® reduces the risk of thromboembolic stroke by one-quarter with a non-significant increase in intracranial bleeding and no difference in deaths [22]. A repeated MRI showed the presence of bilateral subdural hematomas, which obviously was the adverse effect of combined antiplatelet and anticoagulation therapy. On the other hand, such therapy showed no effect on reducing the rate of ischemic strokes, pointing toward the concept that atherosclerotic thrombosis is not the basic mechanism of progressive cerebral arterial stenosis in MMD patients.

Conclusion

One of the major observations that emerge from this case report is that mild neurological symptoms appeared very early in the course of the disease before any other system was clinically affected. Nearly half of SIOD patients have neurologic symptomatology. In such a case, the course of the disease and the final outcome of the patient we presented would, at least partly, be avoided. Finally, with advances in genetic diagnostics, a step forward toward genetic therapy for MMD is reasonably expected.

Informed consent statement

Consent was obtained from the patient's mother for the publication of this report and any accompanying images.

Conflict of interest

The authors declare no conflict of interest.

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Received on August 29, 2021
Revised on February 16, 2022
Accepted on March 1, 2022
Online First March 2022