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# Neurological symptoms in Schimke immuno-osseous dysplasia in a 11-year-old girl: a case report

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*Background: Schimke immuno-osseous dysplasia (SIOD, OMIM 242900) is a rare, autosomal recessive, pleiotropic disease caused by mutations in the SMARCAL1 gene. SIOD is characterized by a triad of symptoms, i.e., progressive kidney disease due to focal segmental glomerulosclerosis (FSGS), spondyloepiphyseal dysplasia and T-cell immunodeficiency. Additionally, heterogeneous neurological symptoms are often observed in the course of the syndrome.*

*Case: The authors describe the case of a 14-year-old girl with SIOD, who presented with recurrent neurological symptoms, such as migraine-like headaches, diplopia and seizures. She was born at 34 weeks of pregnancy with hypotrophy (1280 g) and short stature (44 cm). Nephrotic-range proteinuria, the first symptom of the disease, was detected at the age of 4 and a half years. Significant immunodeficiency was also observed. She was finally diagnosed with Schimke immuno-osseous dysplasia on account of two pathogenic variants, c.836T>C (p.F279S) and c.2542G>T (p.E848X) identified in the SMARCAL1 gene.*

*Conclusions: This report describes the clinical features and neuroimaging findings of a patient with SIOD. It also presents a possible correlation between neurological events and the Schimke disease, which should be considered during the diagnostic process.*

**Keywords:** SCHIMKE IMMUNOOSSEOUS DYSPLASIA; NEUROLOGIC MANIFESTATIONS; GLOMERULOSCLEROSIS, FOCAL SEGMENTAL

## INTRODUCTION

Schimke immuno-osseous dysplasia (SIOD, OMIM 242900) was first described in 1971 by Schimke (1). It is a rare, autosomal recessive, pleiotropic disease caused by mutations in the *SMARCAL1* gene, encoding for the chromatin remodelling enzyme SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1 (2).

Schimke immuno-osseous dysplasia (SIOD) is characterized by a triad of symptoms, i.e., progressive kidney disease due to focal segmental glomerulosclerosis (FSGS), spondyloepiphyseal dysplasia and T-cell immunodeficiency (1, 3, 4). Additional features include disproportionate short stature, bone marrow failure, enhanced atherosclerosis, abnormal dentition, hypothyroidism, thin hair, corneal opacities, cancer, including non-Hodgkin lymphoma and osteosarcoma (3, 5-7), and a variety of neurological symptoms.

The disease spectrum ranges from mild to severe. Neurological manifestations are more often in severely affected patients (5). The most frequently reported symptoms are migraine-like headaches, transient ischemic attacks (TIA) or cerebral ischemia. The cause of ischemic brain incidents is often described as disorganized internal elastic lamina and medial/intimal hyperplasia of the vessels. Predisposing factors are renal disease, systemic hypertension, immune dysfunction, dyslipidaemia, early atherosclerosis, and impaired vascular elastogenesis (8). Some authors presume the exis-

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tence of a correlation between cerebral ischaemia and white matter alterations, moyamoya phenomena, and alterations of cerebellar hemispheres and vermis (9). There have been few reported cases of microcephaly, seizures and mild intellectual disability accompanying SIOD, yet the majority of patients present normal cognitive development (9, 10). However, the underlying pathophysiology of the described neurological events in SIOD remains poorly understood (11).

The authors describe the clinical features and neuroimaging findings of a 14-year-old girl with SIOD and present the associated neurological symptoms.

## PATIENT PRESENTATION

Due to placental abruption, a 14-year-old Caucasian girl was born at 34 weeks of gestational age, from a first pregnancy and first delivery, by caesarian section. The newborn was hypotrophic with a birth weight of 1280 g, birth length of 44 cm and an Apgar score of 9. There was no family history of renal disease. Apart from short stature (< 3rd percentile), the primary manifestation of the Schimke disease, such as nephrotic range proteinuria, hypoalbuminemia, hypogammaglobulinemia and hypercholesterolemia, appeared at the age of 4.5 years. Due to an unclear underlying pathology of glomerulopathy, the decision was made to perform a percutaneous renal biopsy analysis, which revealed minimal-change disease (MCD). Moreover, genetic testing did not confirm the presence of mutations in the *NPHS2* or *WT1* genes, considered to be linked to glomerulopathy. Treatment with methylprednisolone and later cyclosporine A (CsA) was shown to be unsuccessful and the patient's renal function deteriorated. At that time, the girl was also diagnosed with hypothyroidism and the presence of anti-thyroid peroxidase antibodies (anti-TPO) was identified. The thyroid gland appeared normal during the ultrasound examination.

In the course of the treatment with CsA, the girl was hospitalized several times due to severe headaches, nausea and muscle pain. These symptoms were suspected to be side effects of CsA therapy. Laboratory tests, performed during hospitalization, revealed elevated levels of creatine kinase (CK). Brain imaging was within a normal range. The decision was made to discontinue the treatment to reduce long-term side effects.

Moreover, arterial hypertension developed soon after and, at the age of seven, the girl was admitted to the hospital on account of a hypertensive crisis (BP values reached 190/120mm Hg; > 97th percentile). Hypertension was followed by severe headaches, generalized febrile seizures and edema. Due to her persistent impaired consciousness and a visual disturbance, computed tomography was performed, but failed to reveal any pathologies. Anti-hypertensive treatment, including ramipril, clonidine and carvedilol was administered and the patient's condition improved. Her febrile status was secondary to an upper respiratory tract infection.

In the following year, renal function deteriorated rapidly, showing an absence of clinical response to treatment, i.e., generalized edema and persistent hypertension resulted in worsening of the girl's condition. Additionally, respiratory tract infection, headaches and diplopia occurred. Finally, the patient progressed to end-stage renal disease, requiring peritoneal dialysis (PD) at the age of seven, later qualifying for renal transplantation. From that time onwards, disproportionate growth was evident. During the initial cycles of PD, the girl manifested neurological disorders, such as esotropia, appendicular ataxia, dysarthria and the weakening of deep tendon reflexes. Magnetic resonance imaging (MRI) of the brain and an analysis of cerebral spinal fluid excluded organic brain disease, leading to raising the possibility of Miller Fisher syndrome. However, this rare cranial nerve variant of the Guillain-Barré syndrome, occurring usually shortly after viral or bacterial infection, was further excluded.

Progressing renal failure resulted in the need to perform further diagnostic procedures, consequently, FSGS was confirmed in another percutaneous renal biopsy analysis. Owing to persistent proteinuria, bilateral nephrectomy was planned before the renal transplantation.

The clinical outcome overall strongly corresponded to the features of SIOD. Consequently, further genetic tests were performed and the results confirmed the suspicion, i.e., a molecular analysis of a 31-gene panel, linked to the pathogenesis of steroid-resistant nephrotic syndrome disclosed two pathogenic variants c.836T>C (p.F279S) and c.2542G>T (p.E848X) in the *SMARCAL1* gene, which are distinctive for Schimke disease (PodoNet Registry, Clinical Genetics Unit, Department of Biology and Medical Genetics, Medical University of Gdańsk).

At the age of nine and a half years, sevelamer was added to the therapy due to laboratory tests outcome distinctive for end-stage renal disease, including severe hyperphosphatemia.

Laboratory tests in the control examinations repeatedly revealed immunoglobulin G (IgG) deficiency, while immunoglobulin A and M remained within normal range. Given that the described characteristic of SIOD is immunodeficiency, the decision was made to perform an immune system assessment. The outcome showed a reduced complement component C3 and lymphopenia with a reduced percentage and number of CD3, CD4, NKT lymphocytes, increased

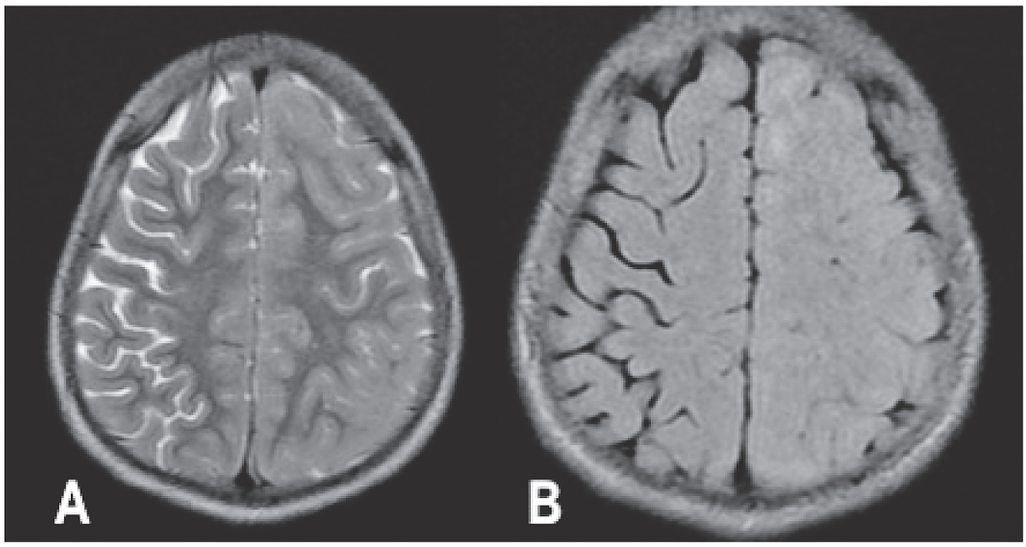


FIGURE 1A, B. **Cerebral MRI of the patient.**

A - SE / T2 sequence; B - FLAIR sequence
Flattening of the sulci and narrowing of the gyri on the left frontal, parietal and temporal lobes, as well as bilaterally in the vicinity of the right frontal cerebral hemisphere.
Compressed subarachnoid space with cortical thickness – the intensity of signals of visible structures mildly increased.

absolute count and percentage of B lymphocytes and slightly reduced lymphocyte function in the blast transformation test.

At the age of ten and half years, the girl was admitted once more to the hospital with neurological symptoms. She presented limited verbal response, right-sided hemiparesis, incoherent speech, nausea and vomiting. As soon as she regained consciousness, she reported a severe headache on the left side. Laboratory tests unveiled severe hyponatremia, hypoalbuminemia and hypophosphatemia. A neurological diagnosis was performed, including computed tomography (CT), MRI, electroencephalography (EEG) and blood flow distribution in cerebral and cervical arteries. Brain imaging did not reveal any pathologies, however, the EEG showed background left-sided slowing, quite numerous, mainly intra-voltage delta waves 2-3c/sec and theta waves 4-6c/sec. Having suspected TIA, acetylsalicylic acid (ASA) in a preventive dose of 50 mg per day was administered.

Six months later, the patient was hospitalized for a Tenckhoff catheter replacement due to a chronic peritoneal catheter exit-site infection. The postoperative period was unburdened. However, in the following days, the girl's neurological condition deteriorated. First, she seemed to be drowsy and confused, lacked logical response, expressed anxiety and purposeless involuntary movements, and later on, a persistent fever. A neurological examination confirmed by positive Kernig's sign, nuchal rigidity, as well as positive Chaddock's sign and Gordon's sign on the right side and bilaterally positive Babinski sign. Laboratory tests revealed

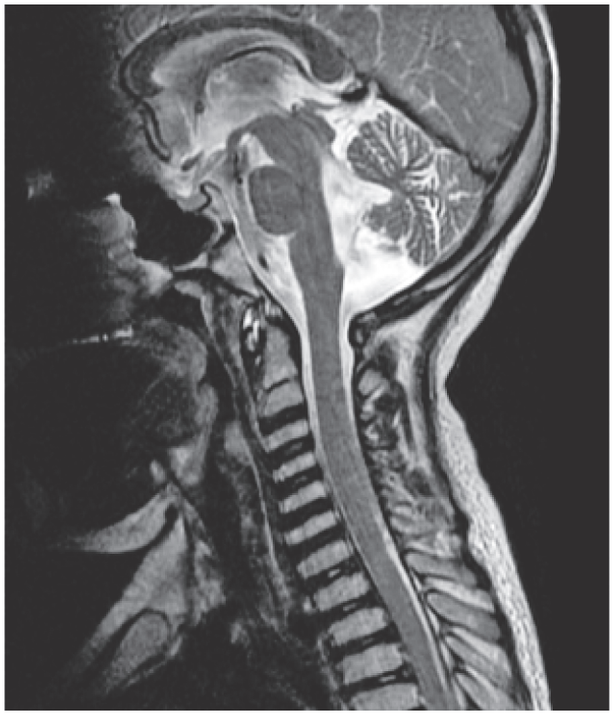

FIGURE 2. **Cervical spine MRI.**

Flattening of the vertebral bodies: height loss and anteroposterior elongation. Normal signal intensity of the bone marrow, normal spinal cord signal intensity.

hyponatremia, so peritoneal dialysis was continued to normalize the electrolyte disorders. Brain imaging was performed to establish a diagnosis, however, amikacin, fluconazole and acyclovir were administered due to the risk of

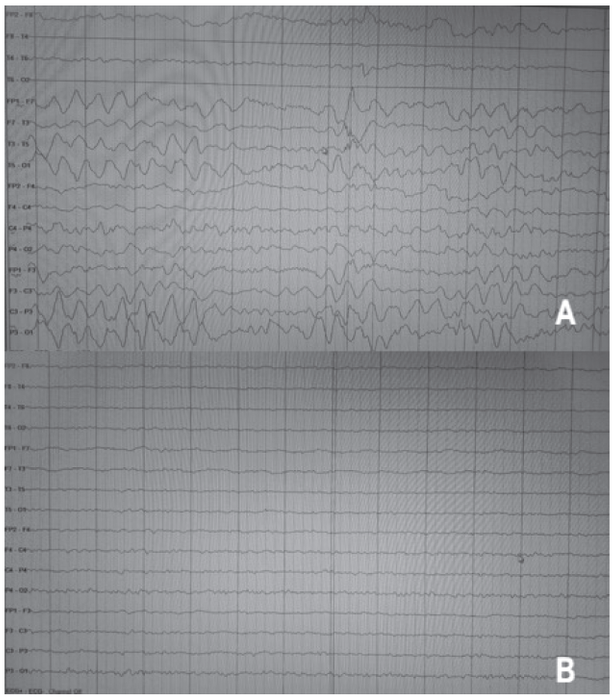


FIGURE 3A, B. **EEG examination outcomes.**

A - EEG revealing disturbances; B - EEG control - outcome within normal range.

TABLE 1. **Neurological symptoms in our patient.**

| Age of the patient | Neurological symptoms | Differential diagnosis |
|---|---|---|
| 5 years old | severe headaches, nausea, muscle pain | side effects of CsA therapy |
| 7 years old | severe headaches, generalized febrile seizures, persistently impaired consciousness, visual disturbance | hypertensive crisis, seizures connected with high body temperature caused by infection |
| 7,5 years old | esotropia, appendicular ataxia, dysarthria, deep tendon reflexes weakening | Miller Fisher syndrome - a rare cranial nerve variant of Guillain-Barré syndrome, occurring shortly after viral or bacterial infection |
| 10.5 years old | limited verbal response, right-sided hemiparesis, incoherent speech, nausea and vomiting, severe left-sided headaches | hyponatremia |
| 11 years old | drowsiness, confusion, lack of logical response, anxiety, purposeless involuntary movements | hyponatremia, neuroinfection |

ongoing encephalitis. The CT revealed cerebral edema features. On the MRI, the flattening of the sulci and narrowing of the gyri on the left hemisphere, compressed subarachnoid space with cortical thickness were confirmed (Figure 1a, b). Moreover, the MRI of the cervical spine showed mildly flattened vertebral bodies, possibly indicating spondyloepiphyseal dysplasia (Figure 2). The decision was made to administer dexamethasone to lower the intracranial pressure, whereas mannitol, as more suitable for the specific therapy, was contraindicated in our patient due to renal insufficiency. The EEG revealed excessive background slowing and numerous left-sided, delta waves with a tendency to generalization (Figure 3a), as concluded by the consulting neurologist, with the brain activity disorders increasing compared to the previous examination. Valproic acid was administered and gave a positive clinical response. In the control EEG, the changes were resolved (Figure 3b). The girl remained under constant care and had a regular evaluation of her nervous system, receiving a proper dosage of valproic acid. Her intellectual development was appropriate for her age.

## DISCUSSION

Neurological involvement in SIOD has been noted in numerous studies, yet no direct cause has been established. A possible aetiopathology of these symptoms lies in *SMARCAL1* gene mutation, given that the gene is highly expressed in the developing adult mouse and human brain, including neural precursor and neuronal lineage cells (9). The general consensus is that malfunctioning of *SMARCAL1* expression may influence immunologic homeostasis and vascular reactivity, as well as inflammation (11). There are several recurring symptoms that can be classified as components of the Schimke syndrome. In the described case, neurological manifestations were frequently present throughout the girl's medical history (Table 1).

The incidence of headaches is far more common among SIOD patients than in the general population. Migraine-like headaches may be derived from intrinsic vascular dysfunction induced by a disturbance in the vascular endothelium and smooth muscle due to a *SMARCAL1* mutations (12). Our patient experienced recurring headaches along with nausea and, in some cases, high blood pressure.

Atherosclerosis in SIOD patients is a common symptom as well, but the direct cause is poorly understood. Some believe that renal failure leading to hypertension and hyperlipidaemia, accompanied by immune dysfunction, might negatively impact the cerebrovascular system [13]. Microscopic vascular pathology may also develop owing to decreased elastin expression, disorganized internal elastic lamina and medial and intimal hyperplasia (14). Intracranial atherosclerotic vascular disease may be linked to reversible

cerebral vasoconstriction syndrome (RCVS). RCVS has been described as a potentially novel mechanism for cerebrovascular complications and headaches in SIOD (12). The presented case introduces several symptoms that RCVS exhibits, such as weeks-long headaches, focal neurologic signs, and occasional seizures.

Seizures have been reported as a neurological manifestation of SIOD. An EEG examination performed in such cases often shows excessive background slowing, rhythmic or polymorphic. However, some patients do not experience clinical seizures before the onset of cerebral ischemia (15). Our patient presented such abnormalities, including background slowing and numerous delta waves, with a tendency to generalization, in subsequent EEGs.

As is shown in this study, performing a differential diagnosis in cases of neurological abnormalities among patients with SIOD is necessary. Various factors interfere with the nervous system, which should always be considered. In the presented case, hyponatremia was a recurring problem as a consequence of renal failure. It was considered a possible source of neurological abnormalities, given that a decrease in sodium concentration leads to headaches, dizziness, impaired concentration and confusion. Accordingly, our patient received constant sodium supplementation to minimize the risk of recurring hyponatremia.

According to the literature and our own experience, we recommend focusing more on neurological symptoms for SIOD and performing early MRI with vessel imaging and perfusion studies to prevent patients from experiencing possible complications from cerebrovascular events. Furthermore, cerebral imaging should be repeated if further neurological events occur.

This report highlights the importance of genetic identification of the disease. It also refers to the fact that neurological symptoms, occurring in patients with SIOD, should be considered as a part of the syndrome (16).

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SAŽETAK

# Neurološki simptomi u Schimkeovoj imuno-koštanoj displaziji u 11-godišnje djevojčice: prikaz slučaja

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*Pozadina: Schimkeova imuno-koštana displazija (SIOD, OMIM 242900) rijetka je autosomno recesivna pleiotropna bolest uzrokovana mutacijama u genu SMARCAL1. SIOD karakterizira trijada simptoma: progresivna bolest bubrega zbog fokalne segmentne glomeruloskleroze (FSGS), spondiloepifizna displazija i imunodeficijencija T-stanica. Osim toga, tijekom sindroma često se bilježe heterogeni neurološki simptomi.*

*Slučaj: Autori opisuju slučaj 14-godišnje djevojčice sa SIOD-om, s ponavljajućim neurološkim simptomima, poput glavobolje nalik migreni, diplopije i napadaja. Rođena je u 34. tjednu trudnoće, s hipotrofijom (1280 g) i niskim rastom (44 cm). Proteinurija nefrotskog ranga, prvi simptom bolesti, otkrivena je u dobi od 4,5 godine. Štoviše, uočena je značajna imunodeficijencija. Konačno joj je dijagnosticirana Schimkeova imuno-koštana displazija zbog dvije patogene varijante, c.836T>C (p.F279S) i c.2542G>T (p.E848X) identificirane u genu SMARCAL1.*

*Zaključci: Ovo izvješće opisuje klinička obilježja i nalaze neuroslika bolesnika sa SIOD-om. Također prikazuje moguću korelaciju između nastalih neuroloških događaja i Schimkeove bolesti, kako bi se uzela u obzir tijekom dijagnostičkog procesa.*

**Ključne riječi:** SCHIMKEOVA IMUNO-KOŠTANA DISPLAZIJA; NEUROLOŠKE MANIFESTACIJE; GLOMERULOSKLEROZA, FOKALNA SEGMENTALNA