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Avascular necrosis in patients with neuromyelitis optica spectrum disorder (NMOSD): a case series report.
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Avascular necrosis in patients with neuromyelitis optica spectrum disorder (NMOSD): a case series report

Jałowa martwica kości u chorych z rozpoznaniem spektrum zapalenia nerwów wzrokowych i rdzenia (NMOSD) – opis serii przypadków

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Abstract

Avascular necrosis is a disorder that often progresses to joint destruction and physical disability within a few months to a few years. Its aetiopathogenesis is related to bone and marrow ischaemia. The main risk factors include mechanical trauma, chronic use of glucocorticoids, alcohol abuse, coagulopathies, and autoimmune diseases. In the authors' opinion, patients diagnosed with neuromyelitis optica spectrum disorder may be particularly at risk of developing avascular necrosis due to the pathomechanism and treatment modalities of this disease. Currently, there is a lack of accurate epidemiological studies on the coexistence of these two conditions. The present study, describing three patients, serves as the foundation for future, extensive research.

Keywords: avascular necrosis, neuromyelitis optica spectrum disorders, NMOSD, AVN, diagnostic criteria

Streszczenie

Jałowa martwica kości ma charakter postępujący, prowadząc do trwałego uszkodzenia stawu oraz niepełnosprawności w ciągu kilku miesięcy do kilku lat. Etiopatogeneza tej jednostki chorobowej związana jest z niedokrwieniem tkanki kostnej i szpiku. Do głównych czynników ryzyka zalicza się przede wszystkim urazy mechaniczne, przewlekłe stosowanie glikokortykosteroidów, nadużywanie alkoholu, koagulopatie oraz choroby autoimmunologiczne. W opinii autorów pacjenci z rozpoznaniem spektrum zapalenia nerwów wzrokowych i rdzenia (*neuromyelitis optica spectrum disorder*, NMOSD) – ze względu na patomechanizm oraz metody leczenia tej jednostki chorobowej – mogą być szczególnie narażeni na rozwój jałowej martwicy kości. Aktualnie brak dokładnych analiz epidemiologicznych współistnienia tych dwóch schorzeń. Niniejsza praca, będąc opisem trzech pacjentów, stanowi zaczynek przyszłych, szerokich badań.

Słowa kluczowe: jałowa martwica kości, spektrum zapalenia nerwów wzrokowych i rdzenia, NMOSD, AVN, kryteria diagnostyczne

INTRODUCTION

Avascular necrosis (AVN) is progressive and debilitating condition leading to permanent joint damage and disability within a few months to a few years, typically affecting the middle-aged population. US epidemiological data estimate the incidence of this disease at 10,000–20,000 new diagnoses per year. AVN can arise from mechanical trauma, alcohol abuse, glucocorticoid use, coagulopathies, and autoimmune diseases (most commonly systemic lupus erythematosus, SLE) (Moya-Angeler et al., 2015). Chronic corticosteroid use and alcohol abuse account for more than 80% of cases (Mont and Hungerford, 1995). Glucocorticosteroids (GCSs) are thought to increase circulating lipids, which promotes the formation of microemboli in bone-supplying arteries, while also leading to an increase in the size and number of adipocytes in the bone marrow, blocking venous outflow. Furthermore, the effect of GCSs on venous endothelial cells has been postulated to lead to stasis, increased intraluminal pressure, and ultimately necrosis (Solomon, 1981). Notably, treatment with prednisone doses lower than 15 to 20 mg/day carries a low risk of AVN (less than 3%) (Mont et al., 2015). However, each dose increase of 10 mg/day may be associated with a 3.6% increase in risk (Dilisio, 2014). AVN seriously affects the patient's quality of life, which is why studying pathogenesis is important for prevention, diagnosis, and treatment.

Neuromyelitis optica spectrum disorder (NMOSD) is a group of rare (0.5–4.4/100,000) inflammatory demyelinating disorders of the central nervous system affecting primarily the optic nerve and spinal cord, and less frequently the brainstem and brain (Pandit et al., 2015). In 2015, Wingerchuk et al. published updated guidelines for the diagnosis of NMOSD. Detection of AQP4-IgG is the key to the diagnosis of the seropositive form of the disease. For NMOSD with negative or unknown AQP4-IgG status, obligatory magnetic resonance imaging (MRI) criteria exist (Wingerchuk et al., 2015). The natural course of the disease is usually severe, with incomplete remissions and residual symptoms persisting after each acute attack. The gold standard treatment for relapses is the administration of methylprednisolone by intravenous infusion or performing plasma exchange (PLEX) (Wingerchuk, 2010). Because of the significant risk of early recurrence of neurological symptoms, treatment is continued for 2–6 months with oral prednisolone at an initial dose of 1 mg/kg b.w. This dose is gradually reduced depending on the patient's clinical condition. However, the phenomenon of steroid dependence is recognised, and patients may require chronic low doses of prednisolone. In seropositive NMOSD, first-line therapies include eculizumab, inebilizumab, or satralizumab. Immunosuppressive drugs recommended for both seropositive and seronegative NMOSD include rituximab, azathioprine, and mycophenolate mofetil, while tocilizumab is used less commonly due to its high cost (Zakrzewska-Pniewska et al., 2023).

CLINICAL CASES

Patient 1

A 36-year-old female with a history of myasthenia gravis (thymectomy in 1999), cervical and lumbosacral discopathy, cervical spine and right shoulder joint injury (2017), right tibia fracture (July 2017), and deep vein thrombosis of the right lower extremity due to heterozygosity of the factor V Leiden mutation (November 2017) was admitted to the Department of Neurology at the University Clinical Centre of the Medical University of Warsaw in January 2018 due to right lower limb paresis and right-sided sensory disturbances. MRI of the cervical segment of the spinal cord showed a longitudinally extensive lesion (4–5 vertebral levels) with abnormal T2 signal and cord swelling with discrete contrast enhancement. Further diagnostic work-up revealed the presence of IgG anti-aquaporin 4 antibodies (IgG AQP4-Ab), leading to a diagnosis of seropositive NMOSD. Corticosteroid treatment was initiated (initially i.v., followed by p.o.). The patient was later qualified for chronic treatment with rituximab (April 2018). In 2020, the patient was diagnosed with AVN of the left femoral and both humeral heads. In June 2020, the patient underwent arthroplasty procedures.

Patient 2

A 22-year-old female with no chronic diseases was first admitted to the Neurology Department in November 2017 due to weakness and hypersensitivity of the left upper limb. MRI of the cervical segment of the spinal cord showed a longitudinally extensive lesion (3 vertebral levels) with abnormal T2 signal and contrast enhancement. MRI of the brain was normal, and no IgG oligoclonal bands (OCBs) or AQP4-Ab were detected. Morphologically and functionally, there were no optic nerve abnormalities (ophthalmoscopic examination and visual evoked potentials were normal). A diagnosis of seronegative NMOSD was made, and treatment with intravenous corticosteroids was initiated. The patient was referred for care at the Department of Neurology at the University Clinical Centre of the Medical University of Warsaw. Over the next few years, there were three relapses requiring treatment with intravenous methylprednisolone infusions and/or plasma exchange, with confirmed MRI activity. The patient was qualified for chronic treatment with rituximab (May 2019). In March 2020, the patient was diagnosed with AVN in both humerus heads and the right femoral head. In April 2021, the patient had a left hip endoprosthesis due to this condition.

Patient 3

A 21-year-old male with a history of nicotinism, traumatic sternal fractures, left knee joint injury, and hypertension was admitted to the Department of Neurology at the University

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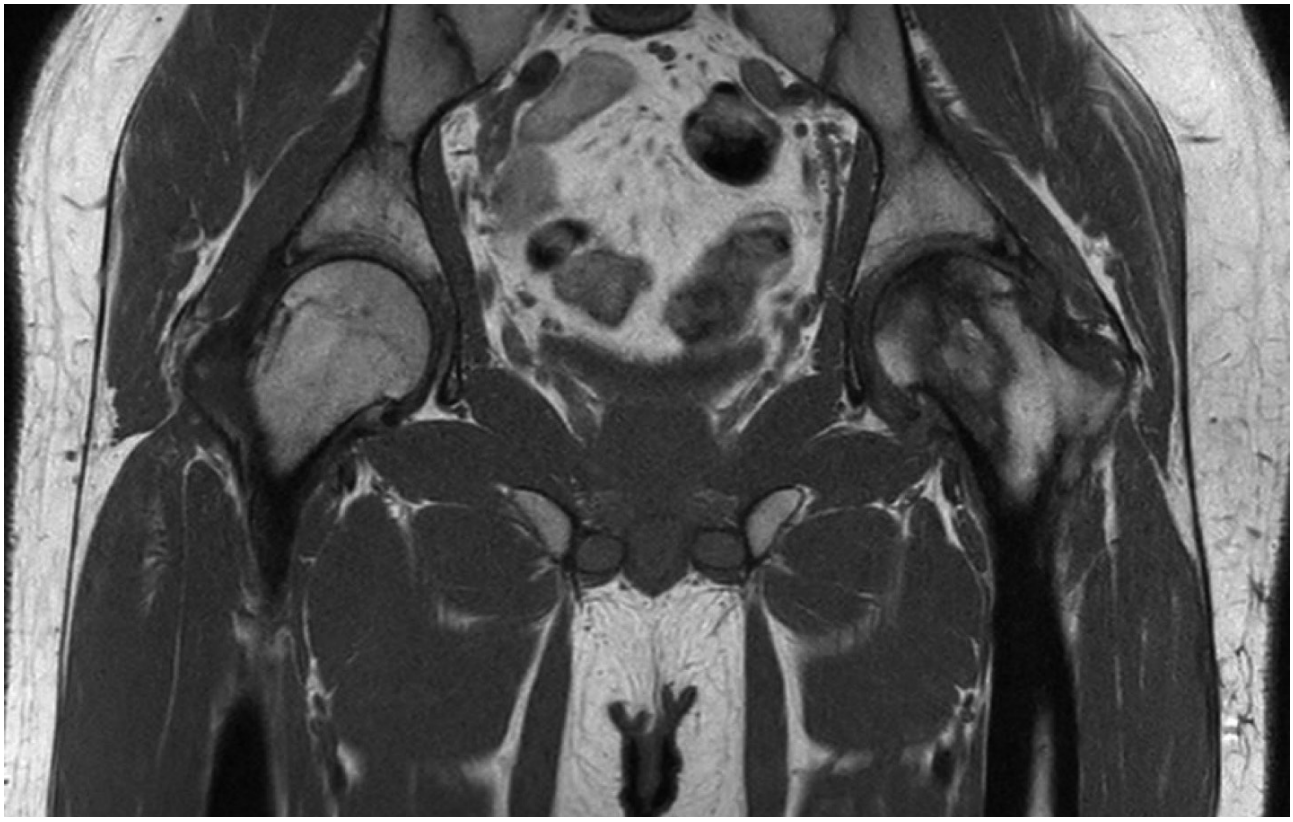

Fig. 1. MRI of the hip joints, coronal T1, April 2021. Area of low signal intensity representing oedema in the left femoral head

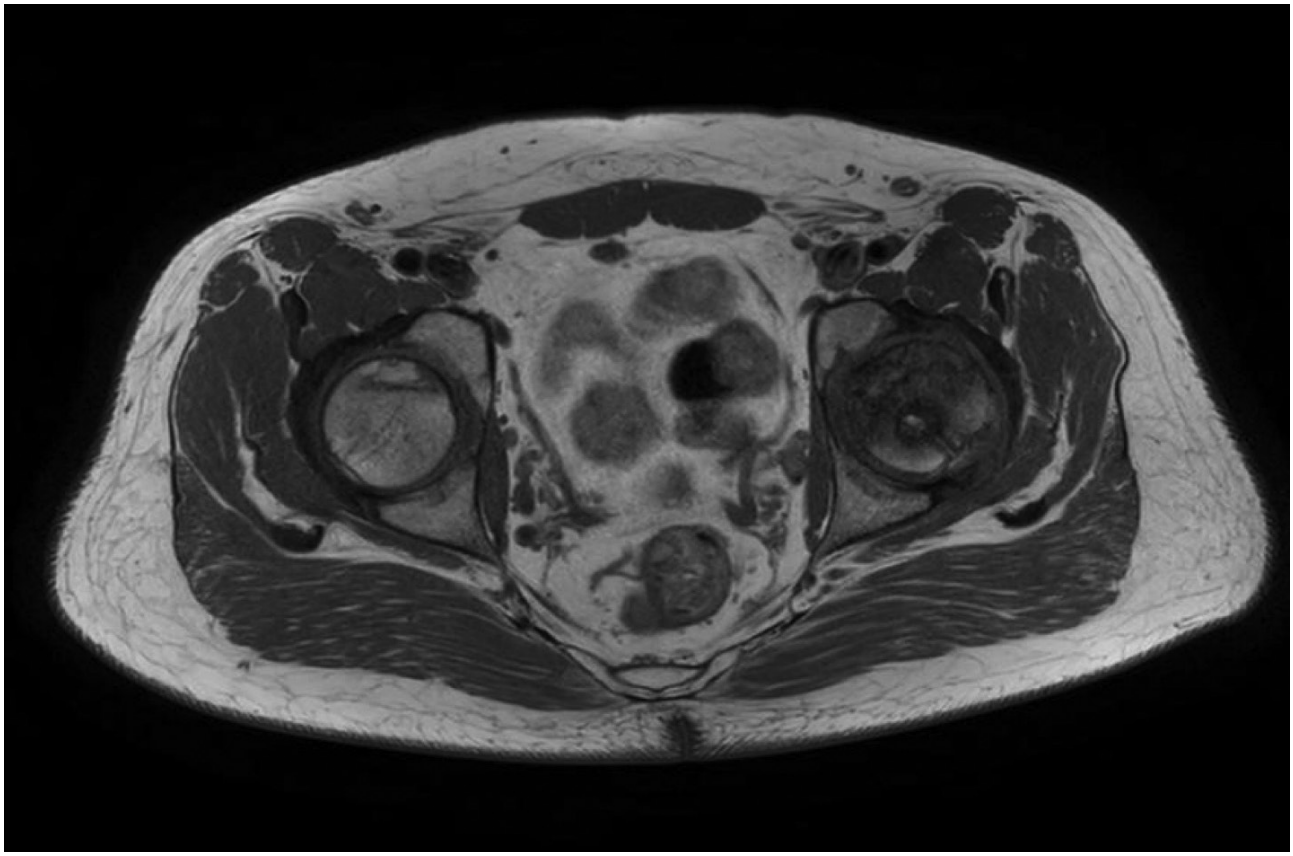

Fig. 2. MRI of the hip joints, axial T1, April 2021. Bilateral abnormal marrow signal intensities in the femoral heads characteristic of AVN

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	Patient 1	Patient 2	Patient 3
Demographic characteristics			
Sex	Female	Female	Male
Age at onset of AVN (year of diagnosis)	39 (2020)	25 (2021)	22 (2021)
Glucocorticoids (prior to diagnosis of AVN)			
Total dose of methylprednisolone i.v.	5 g	15 g	5 g
Methylprednisolone p.o. >20 mg/day (weeks)	2	0	8
Methylprednisolone p.o. <20 mg/day (weeks)	86	152	29
Prednisone p.o. (weeks)	50	No	No
Conditions			
Mechanical trauma	Cervical spine injury Right shoulder joint injury Right tibia fracture	No	Traumatic sternal fractures Left knee joint injury
Autoimmune diseases	Seropositive NMOSD (IgG AQP4-Ab) Seropositive myasthenia gravis	Seronegative NMOSD	Seronegative NMOSD
Coagulopathies	Heterozygosity of the factor V Leiden mutation	No	No
Alcohol abuse	No	No	No
Other	Discopathy	No	Nicotinism Hypertension

Tab. 1. Demographics and risk factors for avascular necrosis in presented patients

Clinical Centre of the Medical University of Warsaw in March 2020 due to right upper limb paresis and sensory disturbances of the right hand and the 4th and 5th fingers of the left hand. In the course of the diagnostic work-up, MRI of the cervical spinal cord showed multiple, partially confluent hyperintense lesions on T2/FLAIR, with the largest lesion (39 mm in length) extending from C3 to C5, exhibiting contrast enhancement. Even though OCBs were detected in the cerebrospinal fluid, MRI of the brain did not show any abnormalities characteristic for multiple sclerosis. Autoantibodies against myelin oligodendrocyte glycoprotein (anti-MOG-Abs) and AQP4-Ab were absent. The patient was diagnosed with seronegative NMOSD, and corticosteroid treatments was started (initially i.v., followed by p.o.). Over the following years, two relapses occurred (December 2020 and March 2021), with confirmed MRI activity. The patient was qualified for chronic treatment with rituximab (May 2021). In 2021, the patient was diagnosed with AVN of both femoral heads (Figs. 1, 2). For this reason, in July 2021 the patient underwent reconstruction of the left hip with administration of autologous growth factors. In February 2022, a follow-up hip MRI showed progression of the left femoral head AVN, and hip arthroplasty was performed in March 2022. The AVN of the right femoral head did not require surgical treatment.

DISCUSSION

In the reported case series, the age at the diagnosis of AVN was consistent with epidemiological data (Moya-Angeler et al., 2015). Interestingly, the average age of patients diagnosed with NMOSD in the literature remains higher (Jarius et al., 2012). However, it is impossible to draw any statistical conclusions, given the small sample size. Two patients had a history of osteoarticular trauma, which is the most common cause of AVN, accounting for more than 20% of cases (Bergman et al., 2019). However, among non-traumatic factors, the most common cause of AVN is GCS use, with a prevalence ranging from 5–25% (Xie et al., 2015). The duration of receiving GCSs varied considerably between our patients. Patient 1 had been using GCSs for over 20 years, while Patient 2 for only about 2 years, and Patient 3 for less than a year. Daily doses remained similar, typically <32 mg/day of methylprednisolone orally. Patient 2 received the highest dose of intravenous methylprednisolone (15 g vs. 5 g). The association between high-dose intravenous pulses of methylprednisolone and the occurrence of AVN has conflicting evidence in SLE studies. An MRI study strongly linked GCS pulse therapy with the early development of silent AVN (Nagasawa et al., 2005). On the other hand, several studies have shown that GCSs pulse therapy is uncorrelated with AVN (Zizic et al., 1985). The risk factors are not limited to GCSs. The first described patient also had thrombophilia due to a factor V Leiden mutation, which, according to Rezus et al. (2021), occurs in approximately 10% of patients with osteonecrosis. Cigarette smoking, found in one of the patients, may also increase the risk (Moya-Angeler et al., 2015). Finally, there are currently no systematic studies on the coexistence of AVN and NMOSD. The described patients ($N = 3$) represent 3.57% of all patients with NMOSD under care of the Department of Neurology at the University Clinical Centre of the Medical University of Warsaw ($N = 84$). However, the true prevalence rate of AVN in our group is likely to be higher, as only symptomatic cases were identified (Tab.1).

SUMMARY

NMOSD is a rare condition, and its diagnosis can be difficult, potentially leading to diagnostic confusion, with irreversible consequences if proper therapy is delayed. However, appropriate treatment may also be associated with numerous complications, including osteonecrosis. Due to the lack of extensive epidemiological studies and in-depth knowledge of the disease's etiopathogenesis itself, there is currently no effective prophylaxis for the adverse effects described. In the authors' opinion, the intensive development of non-corticosteroid immunosuppressive therapies for NMOSD (anti-CD20, anti-IL-6) may reduce the risk of complications related to chronic corticosteroid therapy. However, as the cases of the patients described show, even short-term exposure to corticosteroids may be associated with the development of avascular necrosis. The authors hope that the reported cases will increase awareness of the coexistence of NMOSD and AVN among practising clinicians, both neurologists and orthopaedic surgeons.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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Author contribution

Original concept of study: KMN, BZZP. Collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript: KMN. Critical review of manuscript: APP, MN, RS, BZZP. Final approval of manuscript: BZZP.

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