CANOMAD SYNDROME WITH RESPIRATORY FAILURE

András SALAMON[1], Lívia DÉZSI[1], Bence RADICS[2], Edina Tímea VARGA[1], Tibor HORTOBÁGYI[2], Adrienn TÖMÖSVÁRI[3], László VÉCSEI[1, 4], Péter KLIVÉNYI[1], Cecília RAJDA[1]

[1]Department of Neurology, University of Szeged, Szeged
[2]Department of Pathology, University of Szeged, Szeged
[3]Department of Anaesthesiology and Intensive Therapy, University of Szeged, Szeged
[4]MTA-SZTE Neuroscience Research Group, University of Szeged, Szeged

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CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, M-protein agglutination, disialosyl antibodies) syndrome is a rare polyneuropathy. IgM paraproteins react with ganglioside-containing disialylated epitopes resulting in dorsal root ganglionopathy and B-lymphocyte infiltration of cranial and peripheral nerves. Clinical features include ataxia, slight muscle weakness, areflexia, sensory- and cranial nerve symptoms. Case studies have reported the efficacy of rituximab and intravenous immunoglobulin (IVIg) treatments.

We present the case of a 57-year-old man, who had difficulty walking, with numbness and clumsiness in all limbs. He had areflexia, vibratory sensation loss and ataxia. Laboratory tests showed IgM monoclonal components and disialosyl antibodies in the serum. Nerve conduction studies indicated severe sensorimotor demyelinating polyneuroradiculopathy. Despite IVIg and rituximab treatments, the patient's disease course gradually worsened and he died of respiratory failure. Neuropathological examination revealed dorsal column- and dorsal root atrophy with mixed mononuclear cell infiltration. This article aims to draw attention to this syndrome, and the use of early potent immunosuppressive treatment to improve patients' quality of life.

Keywords: *CANOMAD syndrome, rituximab, respiratory failure, ataxic neuropathy*

LÉGZÉSI ELÉGTELENSÉGGEL JÁRÓ CANOMAD SZINDRÓMA

Salamon A, MD; Dézsi L, MD; Radics B, MD; Varga ET, MD, PhD; Hortobágyi T, MD, PhD; Tömösvári A, MD; Vécsei L, MD, PhD, DSc; Klivényi P, MD, PhD, DSc; Rajda C, MD, PhD

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A CANOMAD (krónikus ataxiás neuropathia, ophthalmoplegia, M-protein-agglutináció, diszialozil-antitestek) szindróma ritka polyneuropathia, melyben IgM-paraproteinek lépnek reakcióba a diszializált epitópokat tartalmazó gangliozidokkal. Ezen folyamat hátsó gyöki ganglionopathiához, valamint a cranialis és a perifériás idegek B-lymphocyta-mediált infiltrációjához vezet.

A betegség klinikai képét ataxia, enyhe fokú izomgyengeség, areflexia, valamint szenzoros eltérések és agyidegtünetek dominálják. A rituximab-, valamint az intravénás immunoglobulin (IVIg-) kezelés hatékonyságát esettanulmányok támasztják alá.

Közleményünkben egy 57 éves férfi beteg járásnehezítettséggel, négy végtagi zsibbadással és ügyetlenséggel járó esetét mutatjuk be. Neurológiai státuszában areflexia, vibrációérzés-csökkenés, valamint ataxia volt megfigyelhető. A laboratóriumi vizsgálatok a szérumban IgM monoklonális komponens és diszialozil-antitestek jelenlétét igazolták. A beteg részletes elektrofiziológiai kivizsgálása során szenzomotoros demyelinisatiós polyneuroradiculopathia igazolódott. Az alkalmazott IVIg- és rituximab-kezelés ellenére a beteg állapota fokozatosan romlott, majd légzési elégtelenség következtében elhunyt. Az elvégzett neuropatológiai vizsgálatok hátsó kötegi és gyöki atrophiát, valamint kevert mononukleáris sejtes infiltrációt mutattak.

A jelen közlemény célja, hogy felhívja a figyelmet a szindrómára, ezáltal elősegítse a betegek életminőségét potenciálisan javító immunszuppresszív kezelés mielőbbi bevezetését.

Kulcsszavak: *CANOMAD szindróma, rituximab, légzési elégtelenség, ataxiás neuropathia*

Correspondent: Cecília RAJDA MD, PhD, Department of Neurology, University of Szeged; 6725 Szeged, Semmelweis u. 6. Phone: (06-62) 545-348, fax: (06-62) 545-597.
E-mail: rajda.cecilia@med.u-szeged.hu

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CANOMAD (chronic ataxic neuropathy ophthalmoplegia M-protein agglutination disialosyl antibodies) syndrome is a rare, chronic, immune-mediated demyelinating polyneuropathy[1]. About thirty cases can be found in the literature[2]. The syndrome is caused by the presence of a specific IgM paraprotein, which reacts with ganglioside-containing disialylated NeuAc(α2-8)NeuAC(α2-3)Gal neural epitopes[3]. There are two main neuropathological features: dorsal root ganglionopathy and a B-lymphocyte-mediated endoneurinal infiltration of cranial and peripheral nerves[4, 5]. The symptoms begin in the 5th-6th decade with a male predominance[1]. Typical clinical presentation includes ataxia, muscle weakness, areflexia, sensory symptoms, pseudoathetoid movements and cranial nerve symptoms[6]. Rarely, it can be associated with respiratory failure[2]. The elevation of IgM protein levels in the serum is characteristic; these paraproteins are often cold agglutinins[1, 7]. The most frequently seen anti-disialosyl antibodies are GD1b, GD3, GT1b and GQ1b[3]. Electrophysiological tests show sensorimotor demyelinating features, with signs of axonal degeneration[3]. The optimal treatment of the disease is unclear. Some case studies have reported the efficacy of rituximab and intravenous immunoglobulin (IVIg) treatment[1–3, 6, 8, 9].

Case report

A 57-year-old man was admitted to our clinic in 2008, with numbness in all limbs, clumsiness and difficulty walking. The only past medical history that was significant was hypertension. Initial neurological examination showed areflexia, vibratory sensation loss and four limb ataxia. Laboratory tests showed slightly elevated creatine kinase levels (210-293 IU/L; normal range: < 195 IU/L) and IgM lambda monoclonal components in the serum. Brain and neck magnetic resonance imaging were normal. Results of multiple repeated electrophysiological studies were compatible with severe sensorimotor demyelinating polyneuroradiculopathy. The cerebrospinal fluid revealed a slightly increased total protein (0.51 g/l) and 7 lymphocytes/mm^3. A detailed hematological examination excluded multiple myeloma (no severe proteinuria, lack of Bence Jones protein in the urine, no plasma cell proliferation in bone marrow, lack of osteolytic lesions). The patient would be classified as "definite" CIDP as defined by EFNS/PNS diagnostic criteria[10]. Due to the lack of signs indicating motor neuron disease, needle exam was not performed early in the course of disease. During the period of acute worsening, the critical condition of the patient did not permit the examination, which would have been informative in order to evaluate axonal loss and rule out motor neuron disease. Following the lack of effect of steroid treatment (100 mg oral prednisone daily, with a gradually decreasing dose, was associated with an inability to walk) and azathioprine treatment (25 mg starting dose; discontinued due to hepatotoxicity), IVIg treatment (0.4 g/kg/day for 5 days every 6 weeks) was initiated. After a moderate improvement (numbness and clumsiness decreased), the patient's disease course slowly worsened (slight all limbs paresis appeared).

Eight years after disease onset, a relapse with autonomic dysfunction, external and internal ophthalmoparesis, hearing loss and finally severe respiratory failure developed. The patient was admitted to the intensive care unit (ICU), due to the need for mechanical ventilation. The patient's neurological symptoms temporarily improved after plasma exchange and IVIg treatment, but shortly thereafter repeated respiratory insufficiency developed. In the ICU, the patient's fingers became pale and cold, suggestive of Raynaud's syndrome and the presence of cold agglutinins. Laboratory tests showed the presence of anti-H cryoglobulins and anti-ganglioside antibodies (positive for GD1b, GD2, GD3, and GT1b) supporting the CANOMAD syndrome. The functions of the third, fourth and sixth cranial nerves (ptosis, gaze weakness) improved, but due to repeated severe respiratory failure, after 72 days, the patient died.

Neuropathological findings

The autopsy of our patient showed severe bronchopneumonia as cause of death. Detailed neuropathological examination was performed. Routine sections from the brain, spinal cord, dorsal root ganglia, trigeminal ganglia, 7th cranial nerve, sural nerve, adrenals, skeletal muscles, internal organs, skin and bone marrow were analyzed **(Figure 1)**. Semi-thin sections were made from the sural nerve, triceps surae muscle and parietal cortex, and studied by electron microscopy. Immunohistochemistry was performed to identify helper and cytotoxic T-lymphocytes, B-lymphocytes, plasma cells and macrophages **(Figure 2)**. Severe dorsal column and dorsal root atrophy **(Figure 1.A)** were found. Mild neuronal loss was observed within the dorsal root ganglia (DRG) accompanied by mixed mononuclear cell infiltration **(Figure 1.B** and **2.A, B, C)**. No B-lymphocytes were found in the DRG **(Figure 2.D)**. Moderate axonal loss was identified in the

cross-sections of the sural nerve with no signs of acute demyelination, necrosis or vasculitis **(Figure 1.C)**. Congo-red staining excluded local and systemic amyloidosis as the cause of neuropathy. No ultrastructural abnormalities were found on the myelin-sheaths. Skeletal muscles exhibited global, but not typical selective type II atrophy **(Figure 1.D)**. Histological examination excluded neurodegenerative diseases of the brain. Neither hematopoietic or lymphoid tumor, nor systemic amyloidosis was found.

Discussion and conclusion

Earlier described CANOMAD cases reported patients with optic nerve involvement, extramembranous glomerulonephritis, and a syndrome of inappropriate antidiuretic hormone secretion (SIADH)[2, 11–14]. Cases without ophthalmoplegia, furthermore, with temporary respiratory failure associated with facial involuntary movements were also mentioned[2, 11–14]. We report a case of CANOMAD syndrome with severe respiratory failure followed by neuropathological evaluation. In another case described in the literature, acute respiratory failure was resolved with IVIg treatment[2]. Despite the stabilization of symptoms after IVIg administration in our patient, persistent severe respiratory failure required additional therapeutic steps (rituximab). One month after the rituximab treatment, the cranial nerve symptoms were partially resolved. The absence of B-lymphocytic infiltration in the peripheral nerves suggests that rituximab may be effective at the histological level. We assume that the patient's death could be explained by the long disease course, and the long stay in ICU, complicated with infections.

In summary, CANOMAD syndrome is a rare sensorimotor, slowly developing polyneuropathy, which predominantly affects middle-aged men and it can be fatal. In the case of a patient with immune-mediated neuropathy, cranial nerve symptoms and Raynaud phenomenon, the physician should consider CANOMAD syndrome. A quick, precise diagnosis allows more rapid initiation of potent immunosuppressive treatment.

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CONFLICT OF INTEREST
None of the authors has any conflict of interest to disclose.

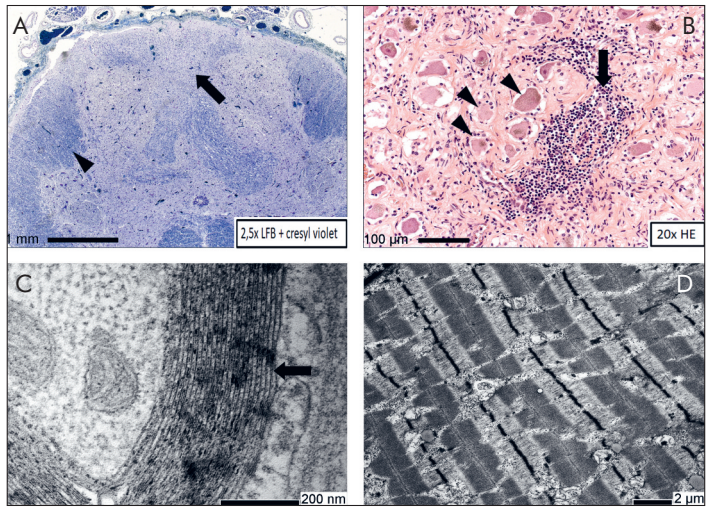

Figure 1. *Neuropathological features of CANOMAD syndrome.* **A** *Light microscope image from the spinal cord. Note the general atrophy of the dorsal column (arrow) in the transverse section of the sacral spinal cord. Loss of myelinated fibers results in faint staining of the gracile fascicle, while the pyramidal tract (arrowhead) is preserved. (Luxol Fast Blue stain + cresyl-violet, magnification 2.5x).* **B** *Mononuclear cell infiltrate (arrow) in the center of a dorsal root ganglion, accompanied by focal loss of ganglion cells. Preserved ganglion cells (arrowhead) are visible around the inflammatory infiltrate. (HE stain, 20x magnifictaion).* **C** *Regular myelin sheath (arrow) around an axon from the sural nerve. No immunocomplex deposits, amyloid fibrils or structural alterations of the myelin sheath were found (x200 nm).* **D** *Electron microscopy of the skeletal (intercostal) muscle – global muscle atrophy (x2 µm). (CD – cluster of differentiation)*

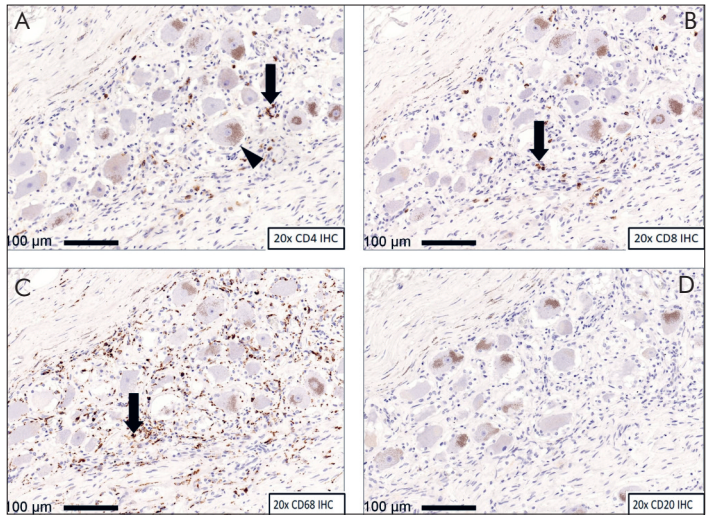

Figure 2. *Mixed mononuclear infiltration of the dorsal root ganglia.* **A** *CD4+ immunohistochemistry reveals helper T-lymphocytes (arrow). Brown granules in the ganglion cells are intracytoplasmic melanin and lipofuscin pigments (arrowhead).* **B** *CD8+ immunohistochemistry shows cytotoxic T-lymphocytes (arrow).* **C** *Most of the mononuclear cells are CD68+ macrophages (arrow).* **D** *CD20+ B-lymphocytes were not found. (CD – cluster of differentiation)*

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