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Case report

Flaccid paralysis in neuromyelitis optica: An atypical presentation with possible involvement of the peripheral nervous system

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ABSTRACT

Background: Neuromyelitis optica spectrum disorders (NMOSD) typically lead to spastic paraparesis and spare the peripheral nervous system (PNS).
Case report: Here, we describe an anti-aquaporin-4-seropositive NMOSD patient suffering from acute transverse myelitis with painful, flaccid paralysis and incontinence of urine and feces. Due to the involvement of the PNS as indicated by electrodiagnostic examination, we verified the expression of aquaporin-4-channels on the proximal dorsal spinal radix of rats by staining rat tissue with human NMOSD serum.
Conclusion: This case suggests a manifestation of the proximal PNS in NMOSD. Thus, NMOSD should be considered as a differential diagnosis for patients presenting with signs of spinal cord disease and additional radicular involvement.

1. Background

Neuromyelitis optica spectrum disorder (NMOSD) refers to a group of antibody-mediated inflammatory diseases of the central nervous system (CNS). Typically, demyelinating lesions manifest in the optic nerve, spinal cord, area postrema, brainstem, and diencephalon. This leads to spastic paraparesis, and visual and sensory deficits (Wingerchuk et al., 2015). While NMOSD sometimes manifest in muscles leading to hyper-CK-aemia (Iyer et al., 2014), they typically spare the peripheral nervous system (PNS). A higher incidence of carcinoma in NMO patients, especially in elderly patients, has been described (Ontaneda and Fox, 2014).

2. Case report

We present here an atypical case of NMOSD. A 75-year-old woman had suffered from four episodes of paralysis of the lower limbs for the past ten months with incomplete response to repeated methylprednisolone therapy. In the first episode, the patient had pain and weakness of the left leg, resulting in the inability to walk. This was accompanied by fecal and urinary incontinence. Furthermore, she showed decreased left patellar reflex with intact right patellar reflex and Achilles tendon reflexes on both sides. On MRI, transverse myelitis at T12/L1 was visible. Following treatment with methylprednisolone (cumulative dose of 5 g intravenously), the clinical symptoms completely recovered. In the second episode, paralysis was incompletely responsive to methylprednisolone therapy. The patient was able to stand without help but could not walk after this episode. From here on, all reflexes of the lower limbs were reduced or absent with persistent flaccid paraparesis until end of follow-up. The third episode was characterized by hypoesthesia in the left part of the face corresponding to a demyelinating lesion in the medulla oblongata that recovered after steroid therapy. The last exacerbation of pain and weakness of both legs had started 9 days before presentation in our hospital. The patient was unable to stand. Her muscle power reached a score of 2 of 5, 0 of 5, 3 of 5, and 0 of 5 for right hip flexion, left hip flexion, right foot dorsiflexion, and left foot dorsiflexion respectively based on the British medical research council (MRC) scale, accompanied by flaccid tonus. Deep tendon reflexes were absent in the lower limb and increased in the upper limb. She had complete loss of bowel and bladder function with incontinence of urine and feces. Interestingly, the patient had suffered from a malignant B-cell Non-Hodgkin lymphoma 16 years ago, which had been treated with radiation followed by 8 years of rituximab. Besides the lymphoma, she suffered from arterial hypertension, vitamin D deficiency, unilateral kidney atrophy (with normal renal function parameters), and osteopenia. She had no diabetes.

We conducted electrodiagnostic examinations and she was diagnosed with a predominantly axonal sensorimotor polyneuropathy with

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Table 1
Motor nerve conduction study (NCS) of the left tibial nerve revealed slightly reduced nerve conduction velocity (NCV) (38.6 m/s) and amplitude reduction (0.6 mV). Sensory NCS of the left sural nerve showed reduced amplitude (1.7 μV), while NCV was normal. Motor NCS of the left median and ulnar nerves revealed an amplitude reduction (2.9 and 3.9 mV, respectively) and slightly reduced NCV of the median nerve (48.1 m/s), while ulnar NCV was normal. Sensory NCS showed slightly reduced NCV (42.2 and 42.6 m/s, respectively) and normal amplitudes. Furthermore, F-wave loss, but no chronodispersion was found (ND = not detected). On electromyography (EMG) of the left tibialis anterior muscle spontaneous discharges (positive sharp waves (PSW) and fibrillation potentials) were detected.

Motor NCS	Distal motor latency [ms]	Amplitude [mV]	NCV [m/s]	F wave latency
median nerve	4.8	2.9	48.1	ND
ulnar nerve	3.8	3.9	50.7	ND
tibial nerve	7.2	0.6	38.6	—
Sensory NCS	Latency [ms]	Amplitude [μV]	NCV [m/s]	
median nerve	3.7	15	42.2	—
ulnar nerve	2.7	11	42.6	—
sural nerve	3.2	1.7	46.6	—
Muscle	Fibrillation	PSW		
left tibialis anterior muscle	3/10	2/10	—	—

absent F waves (Table 1). Magnetic resonance imaging of the spinal cord showed two gadolinium-enhancing intramedullary lesions, C6/7 to T9 and T12 to the conus medullaris (Fig. 1(A)). In the cerebral spinal fluid, an increased protein (803 mg/dl) without pleocytosis was found. There were no oligoclonal bands and IgG-class antibodies against measles, rubella, and varicella-zoster virus. Visual acuity was reduced to 20% on both sides and the visual evoked potentials showed delayed latencies (p100: left 147.5 ms, right 140.5 ms). The serum-titer of aquaporin-4 (AQP-4)-antibodies was positive (1:320, cell-based assay, Prof. Stöcker, Lübeck, Germany, cut-off 1:10), which confirmed the diagnosis of NMOSD.

Due to higher age of the patient at first manifestation, history of lymphoma, and possible association of NMOSD and malignancies (Pittock and Lennon, 2008), computer tomographies of the neck, thorax, and abdomen had been performed at her first episode of paralysis (10 months ago) to exclude malignancy. Furthermore, we conducted x-ray of the chest and ultrasound of the abdomen during the fourth described episode of the disease. We also analyzed the CSF histologically for atypical cells, performed immunophenotyping via flow cytometry, and excluded clonality. During the whole follow-up as well as at the present examination, there was no evidence of further malignancy or recurrence of the lymphoma. Furthermore, immunoreactivities of anti-onconeuronal antibodies (against amphiphysin, CV2, PNMA2, Ri, Yo, Hu, REC, SOX1, Titin, Zic 4, GAD65, and DNER, performed in the laboratory of prof. Stöcker, Lübeck, Germany) were absent.

Our patient showed a limited therapeutic response to intravenous steroids. Therefore, we conducted therapeutic apheresis (5x immunoadsorption, 1x plasmapheresis). Right leg paresis improved from 2 to 3 of 5 MRC but remained flaccid. Furthermore, we induced a selective immunosuppression with the anti-CD20-antibody rituximab (1000 mg intravenously).

Since our patient had the unusual combination of a confirmed demyelinating CNS-disorder with clinical and electrodiagnostic involvement of the PNS, we explored the possibility that NMOSD might also involve parts of the PNS, particularly the radix. We stained the spinal cord and proximal radix including dorsal root ganglia of 8 weeks old male Sprague Dawley rats with serum of another AQP4-seropositive NMOSD patient without peripheral involvement (titer 1:10.000). Unfortunately, we were unable to use the serum of the presented patient because her pre-apheresis specimen had already been exhausted for diagnostic purposes and her post-treatment antibody titer was too low to adequately address our clinical question. Six micrometer-thick cryosections (coronal slice) of murine radix and dorsal root ganglion were fixed in acetone and blocked for unspecific binding with 0.1 M

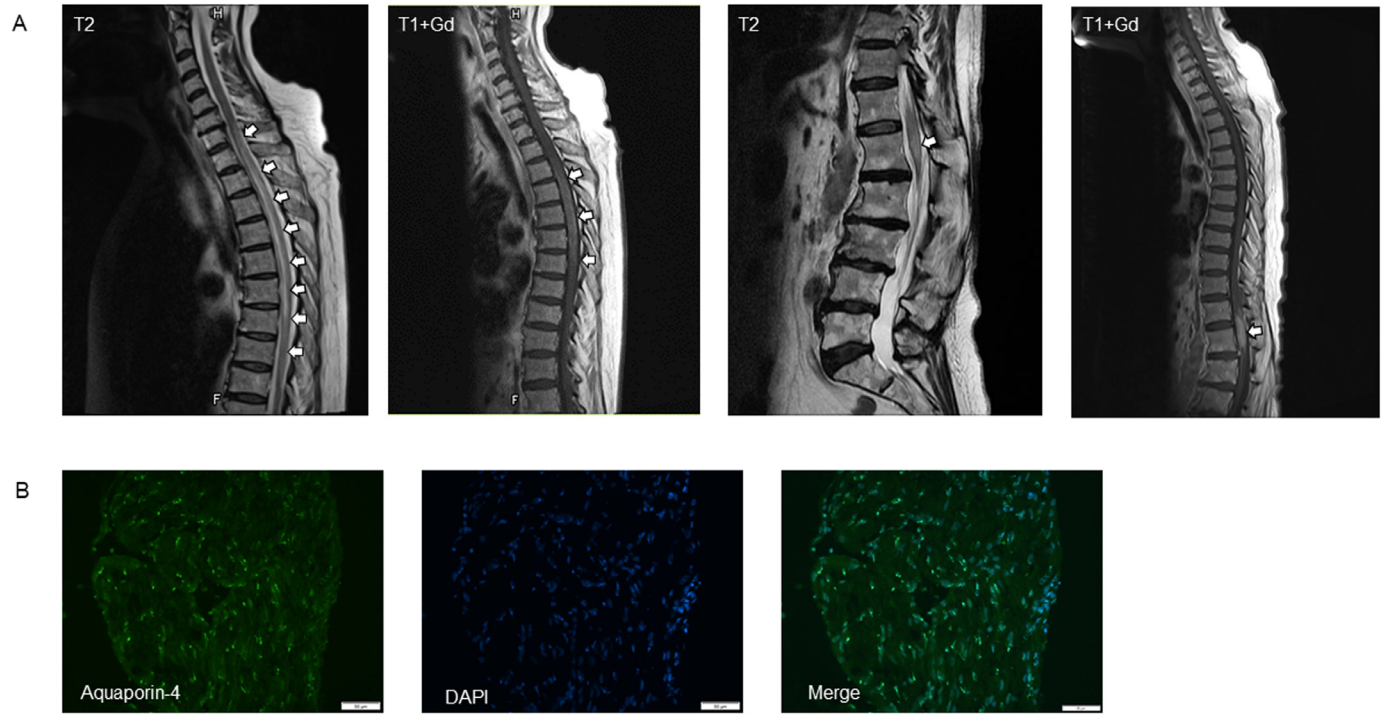

Fig. 1. A: T2 and gadolinium-enhanced T1-weighted spinal MRI of the thoracic and lumbal region demonstrating longitudinally extensive myelitis (C6/7 to T9 and T12 to the conus medullaris). B: AQP4 staining (green) with human AQP4-antibody-containing serum on the proximal part of a murine, cervical radix and DAPI-staining (blue).