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Combined central and peripheral demyelination – one-year follow-up of patient with co-incidence of multiple sclerosis and multifocal acquired demyelinating sensory and motor neuropathy – A Case Report

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Abstract

Combined central and peripheral demyelination (CCPD) is a rare autoimmune neurologic disease, characterized by immune-mediated damage of myelin sheath at central and peripheral levels of the nervous system. The current knowledge about this disorder is only limited, mainly due to the low incidence of the disease. According to previous studies, CCPD has a very heterogeneous course, insufficient therapeutic response, and an unfavorable prognosis. We report on the 37-year-old patient with a coincidence of demyelinating lesions in the brain fulfilling current McDonald's diagnostic criteria for multiple sclerosis, as well as the presence of an atypical variant of chronic inflammatory demyelinating polyneuropathy (CIDP) – multifocal acquired demyelinating sensory-motor neuropathy (MADSAM), as a subtype of combined central and peripheral demyelination (CCPD).

CASE REPORT

INTRODUCTION

Autoimmune demyelinating diseases include a wide spectrum of diseases that are associated with immune damage to myelin sheath, including for example multiple sclerosis (MS) or CIDP. Current knowledge about combined central and peripheral demyelination is so far limited. The largest study to date retrospectively followed 31 patients and reported a significantly heterogeneous course, insufficient therapeutic response, and an unfavorable prognosis (Cortese *et al.* 2016). To the best of our knowledge, different disease phenotypes of CCPD have not been evaluated, yet. We report on a patient with a coincidence of multiple sclerosis according to McDonald´s 2017 diagnostic criteria for MS (Thompson *et al.* 2018) and the atypical variant of CIDP – multifocal acquired demyelinating sensory-motor neuropathy (MADSAM).

CASE PRESENTATION

A 37-year-old Caucasian male was admitted to our neurologic department in November 2021 with a history of multiple asymmetric sensory complaints developed over two years, e.g., intermittent paraesthesias on the fingers of the right hand, intermittent visual flashes in the peripheral visual field, neuralgiform trigeminal pain in the left facial area, dysaesthesias on the left shoulder as well as neck and lumbar back pain. The patient's personal history was unremarkable, the patient was being treated for arterial hypertension, with no recent history of an infectious disease. On neurologic examination, the patient presented with global hyperreflexia, pathologic pyramidal reflexes - Babinski and Hoffman signs bilaterally, as well as absent abdominal skin reflexes. Approximately three months prior to admission patient underwent a brain and cervical spinal cord MRI, that showed multiple demyelinating lesions within the white matter of the brain in periventricular, juxtacortical, and infratentorial locations, without any post-contrast enhancement (Figure 1A). The location of those multifocal demyelinating lesions fulfilled the revised 2017 McDonald's diagnostic criteria for dissemination in space for multiple sclerosis. The examination of visual evoked potentials confirmed demyelinating lesions bilaterally with prolonged latencies within the optic nerves.

Cerebrospinal fluid (CSF) analysis revealed proteinocytologic association, significant hyperproteinorrhachia (2175 mg/l), mononuclear pleocytosis (42/mm^3), cytologic examination confirmed the presence of lymphocytes, monocytes, and isolated lymphoplasmacytic cells. The immune electrophoresis of CSF confirmed the presence of intrathecal synthesis of oligoclonal bands. The serologic examination of the cerebrospinal fluid (HIV, HSV 1,2, EBV, CMV, Borrelia species), as well as the examination of antiganglioside and antineuronal antibodies, anti-MOG, anti-MAG or aquaporin-4 antibodies, were negative.

Due to the significantly elevated proteins within CSF, we performed another contrast-enhanced MRI of the brain and cervical spinal cord during the hospital stay. The results did not reveal any new demyelinating lesions. However, the post-contrast enhancement of cranial nerves and cervical spinal roots was present.

In order to visualize the whole spinal cord, we performed an MRI of the rest of the spinal cord, where post-contrast enhancement of cauda equina was confirmed, suggesting diffuse involvement of spinal nerves – polyradiculoneuritis (Figure 1B).

To assess the severity of polyradiculoneuritis, we performed nerve conduction studies showing asymmetric demyelination of motor and sensory nerves with conduction block of the right median nerve, pathologic conduction velocity of the right ulnar and right tibial nerve, absent F waves of fibular nerves bilaterally together with prolonged minimal F wave latency of right tibial nerve, as well as absent sensory nerve action potential of right sural nerve (Table 1,2). Due to these markedly asymmetric findings, together with imaging and laboratory results, an atypical variant of CIDP – MADSAM (multifocal acquired demyelinating sensory-motor neuropathy) was concluded.

Regarding combined CNS and PNS involvement, the patient was diagnosed with a co-incidence of MS and an atypical variant of CIDP – MADSAM.

The differential diagnosis of polyradiculoneuritis included serological testing to rule out an infectious etiology (syphilis, bartonellosis, brucellosis, toxocariasis, toxoplasmosis) with a negative result. Due to the presumed autoimmune origin of polyradiculoneuritis, we subsequently started treatment with intravenous immunoglobulins at an initial dose of 2 g/kg of body weight. Afterward, the patient was discharged to outpatient care. We continued therapy using maintenance doses of intravenous immunoglobulins on a monthly basis for next 12 months.

In order to assess the efficacy of treatment, we performed a follow-up MRI of the brain and spinal cord with a contrast agent after 6 months since the

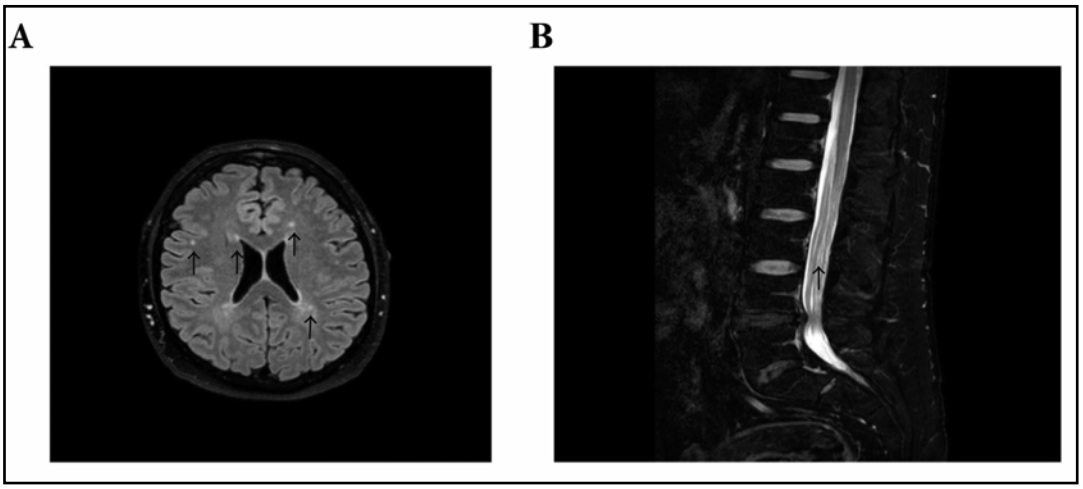

Fig. 1. Baseline MRI of the brain: (A) Multifocal demyelinating lesions within the white matter of the brain 3 months before the admission (arrows); (B) Baseline MRI of the lumbar spinal cord: Pathologic enlargement and post-contrast enhancement of cauda equina at the time of admission

Tab. 1. Nerve conduction parameters of motor nerves at the time of admission

	DML [ms]	CV [m/s]	CMAP amplitude [mV]	F wave latency [ms]
Tibial nerve R	3.9	37.6	8.2	56
Tibial nerve L	5.5	42.5	4.9	50
Fibular nerve R	5,4	45.2	3.0	x
Fibular nerve L	5,2	43.7	1.53	x
Median nerve R	5.5	Conduction block	3.9	24.6
Median nerve L	5.5	51.7	3.3	24.9
Ulnar nerve R	3.9	48.8	3.9	27.9
Ulnar nerve L	4.4	53.4	6.5	26.8

DML – distal motor latency, CV – conduction velocity, CMAP – compound muscle action potential, R- right, L- left

time of hospital admission. The imaging results did not reveal any progression of the coincide conditions, without the presence of new demyelinating lesions in the brain or cervical spinal cord. The post-contrast enhancement of cranial nerves, cervical and lumbar spinal roots persisted. On the other hand, we observed an improvement of the clinical status of the patient, with an improvement of sensory complaints since the beginning of treatment. Follow-up nerve conduction studies showed improved conduction velocity of motor nerves in the upper limbs, the conduction block on the right median nerve completely resolved, conduction velocities in lower limbs remained approximately unchanged (Supplementary Table 1).

Due to the persistence of cranial and spinal nerves inflammation on imaging studies we considered administering natalizumab as an immunomodulatory treatment to improve the clinical outcomes. Our reasoning was based on published data in isolated case reports of the positive efficacy of natalizumab in patients with refractory CIDP (Vallat *et al.* 2015). In this study, natalizumab demonstrated higher efficacy for disease control in patients with CIDP resistant to first-line treatment. Unfortunately, since our patient had high titers of antibodies against John-Cunningham virus (JCV; 2.74 units), natalizumab was contraindicated in order to prevent the development of progressive multifocal leukoencephalopathy (PML). Therefore, we continued the patient on intravenous immunoglobulins, mainly because of improved electrophysiological and clinical parameters.

Subsequently, the patient underwent another follow-up MRI of brain and spinal cord after 12 months since the admission, revealing new juxtacortical demyelinating lesion within the white matter of the brain at the proximity to the left insula (Figure 2A). Furthermore, a new demyelinating lesion without post-contrast enhancement was observed at the left optic nerve, suggesting a prior episode of optic neuritis (Figure 2B). The follow-up MRI of lumbar spinal cord after 12 months since the admission did not show any radiologic improvement (Figure 2C). From the clinical point of view, the patient experienced a complete resolution of symptoms and was asymptomatic. The conduction nerve studies showed conduction velocity on both upper and lower extremities within normal limits, supporting the clinical improvement of the patient (Supplementary Table 2,3).

DISCUSSION

Multiple sclerosis (MS) and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) are two distinct neurological disorders that affect the central and peripheral nervous systems, respectively. The overall prevalence of MS in Central Europe ranges approximately from 62/100,000 to 128/100,000 depending on various studies (Kingwell *et al.* 2013).

Tab. 2. Nerve conduction parameters of sensory nerves at the time of admission

	DSL [ms]	CV [m/s]	SNAP amplitude [uV]
Sural nerve R	x	x	x
Sural nerve L	4.2	42.3	5.5
Median nerve R	4.3	45.9	6.1
Median nerve L	3.8	53.0	5.5
Ulnar nerve R	3.8	52.6	4.1
Ulnar nerve L	3.7	54	3.9

DSL – distal sensory latency, CV – conduction velocity, SNAP– sensory nerve action potential, R- right, L- left

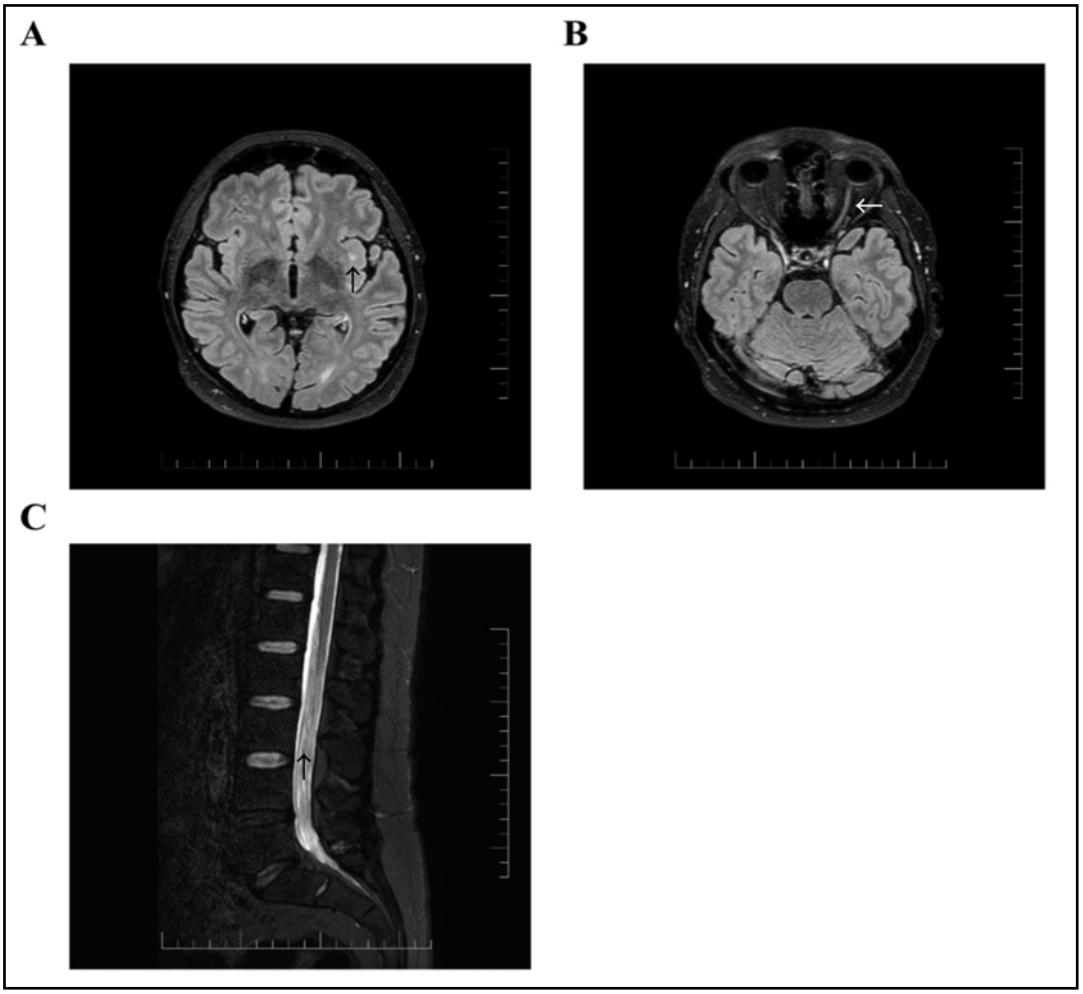

Fig. 2. Follow-up MRI of brain (12 months after the admission): (A) New hyperintense T2 juxtacortical lesion at the proximity to left insula (arrow); (B) Follow-up MRI of brain (12 months): New hyperintense T2 lesion at left optic nerve, without post-contrast enhancement (arrow); (C) Follow-up MRI of lumbar spinal cord (12 months after the admission): Persistent finding of contrast-enhancement of cauda equina (arrow)

The exact prevalence of MADSAM variant is not known. However, CIDP itself is a rare disease with a reported prevalence of 0.7 to 10.3 cases per 100,000 people (Broers *et al.* 2019). Furthermore, atypical variants of CIDP constitute only about 18% of the total fraction of patients (Doneddu *et al.* 2019). Therefore, the probability of co-incidence of MS with a prevalence of 62/100,000 and MADSAM with a calculated prevalence of 0,13/100,000 is approximately 8,06 individuals per 10 billion people, further emphasizing the uniqueness of our case.

Atypical variants of CIDP differ from the classic form not only on the basis of different clinical and electrophysiological parameters but also because of their different therapeutic response - partly due to variable pathological mechanisms of individual atypical variants of CIDP. In general, atypical variants of CIDP represent a worse prognosis, poor therapeutic response, and delayed remission of the disease. First-line therapy for CIDP includes intravenous immunoglobulins, corticosteroids, or plasmapheresis. Previous studies have shown that positive therapeutic response to first-line treatment in patients with MADSAM, as one of the atypical variants of CIDP, is up to about 75% (Viala *et al.* 2004) . Resting approximately 25% of patients with MADSAM are thus refractory to first-line therapy. Although prospective data regarding the effectiveness of second-line therapy for CIDP is missing, there are limited reports from case reports regarding the therapeutic effect of natalizumab, fingolimod, or rituximab as second-line immunomodulating treatment (Vallat *et al.* 2015; Hughes *et al.* 2018; Savasta *et al.* 2017). To be precise, the effect of natalizumab was evaluated in a study including three patients with treatment-refractory CIDP. The results showed significant improvement of clinical condition in two patients and stabilization of clinical condition in one patient. Despite of anecdotal experience of natalizumab being efficacious for both MS and MADSAM, we resigned from its use due to the high titer of antibodies against the JC virus and the increased risk of PML.

CONCLUSION

In conclusion, this case report highlights the diagnostic and therapeutic challenges associated with the co-incidence of MS and an atypical variant of CIDP – MADSAM. The patient presented with multiple asymmetric sensory complaints and was initially diagnosed with MS based on imaging studies and laboratory

findings, which were later supplemented with nerve conduction studies and further laboratory findings to diagnose CIDP-MADSAM. Our case report presents a unique phenotype variant of CCPD, which to our knowledge has not been published before.

As already mentioned, CCPD has a heterogeneous course and insufficient therapeutic response. The main clinical outcome from our case report is the importance of targeted treatment for individual disease phenotypes. The administration of intravenous immunoglobulins lead to significant improvement in clinical and electrophysiological outcomes. On the other hand, the autoimmune demyelination observed in CNS was not fully under control, possibly due to different mechanism of action of intravenous immunoglobulins, targeting more specifically inflammation at the peripheral nervous system. Further studies have to be conducted to determine the optimal therapeutic approach in such cases.

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SUPPLEMENTARY MATERIAL

Supp. Tab. 1. Follow-up nerve conduction parameters of motor nerves (after 6 months)

	DML [ms]	CV [m/s]	CMAP amplitude [mV]	F wave latency [ms]
Tibial nerve R	4.4	37.6	6.5	52.1
Tibial nerve L	4.9	37.3	6.0	50.4
Fibular nerve R	5.6	43.8	3.1	60.0
Fibular nerve L	5.2	42.0	5.1	54.1
Median nerve R	4.2	48.0	4.2	25.7
Median nerve L	4.3	50.4	1.8	25.1
Ulnar nerve R	3.2	52.7	7.8	27.1
Ulnar nerve L	3.6	54.0	6.5	25.6

DML – distal motor latency, CV – conduction velocity, CMAP – compound muscle action potential, R- right, L- left

Supp. Tab. 2. Follow-up nerve conduction parameters of motor nerves (after 12 months)

	DML [ms]	CV [m/s]	CMAP amplitude [mV]	F wave latency [ms]
Tibial nerve R	4.3	38.9	9.3	52.7
Tibial nerve L	7.2	37.2	8.6	48.5
Fibular nerve R	4.7	41.6	5.1	51.6
Fibular nerve L	4.3	40.7	3.9	x
Median nerve R	4.1	57.9	6.9	25.8
Median nerve L	4.1	51.5	6.4	26.0
Ulnar nerve R	3.2	55.8	7.3	27.2
Ulnar nerve L	3.1	56.8	6.1	26.0

DML – distal motor latency, CV – conduction velocity, CMAP – compound muscle action potential, R- right, L- left

Supp. Tab. 3. Follow-up nerve conduction parameters of sensory nerves (after 12 months)

	DSL [ms]	CV [m/s]	SNAP amplitude [uV]
Sural nerve R	2.7	55.6	2.4
Sural nerve L	3.4	43.6	3.9
Median nerve R	3.2	49.3	6.2
Median nerve L	3.0	53.6	4.3
Ulnar nerve R	3.0	56.8	6.0
Ulnar nerve L	2.6	57.6	11.9

DSL – distal sensory latency, CV – conduction velocity, SNAP– sensory nerve action potential, R- right, L- left