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Combined effect of medical therapy and rehabilitation in Chronic Ataxic Neuropathy with anti-Disialosyl IgM Antibodies (CANDA): a case report

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Abstract

Chronic Ataxic Neuropathy with anti-Disialosyl IgM Antibodies (CANDA) is a rare form of immune-mediated sensory ataxic neuropathy. We describe the case of a 45-year-old man, who was diagnosed with CANDA in October 2018. Since then, he has been treated with monthly courses of intravenous immunoglobulin administration (IV Ig) and, in October 2022, he underwent plasmapheresis, reporting a sudden worsening of clinical and motor picture. After a new IV Ig cycle admission, the patient was hospitalized to perform intensive rehabilitation, involving two individual sessions per day (90 minutes each) for 5 days a week. During hospitalization it was registered a relevant improvement in the muscle strength of the lower limbs (LLs). Furthermore, progressive improvements were recorded both in patient's motor performance and in his level of autonomy in activities of daily living. These results had a positive impact on his quality of life and made it possible to reduce the frequency of IV Ig treatments. This is the first case in literature reporting the combined effect of rehabilitation treatment and medical therapy in CANDA neuropathy.

Key Words: chronic ataxic neuropathy; CANDA; anti-disialosyl antibodies; rehabilitation; muscle exercise.

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Chronic Ataxic Neuropathy with anti-Disialosyl IgM Antibodies (CANDA) is a rare form of immune-mediated sensory ataxic neuropathy characterized by a progressive and severely disabling course, sensory deficit-related gait disturbance, hypo-/areflexia and anti-GD1b IgM antibody positivity.[1, 2] Most patients are males; the mean age at onset is 55 years.[3] The most accredited etiopathogenetic theory suggests that CANDA is induced by lesions of the node of Ranvier. Specifically, this autoimmune peripheral neuropathy is associated with disialosyl antibody activity against gangliosides found in the axolemma of the paranode;[4] therefore, it could be classified as a paranodopathy.[5] Most patients affected by CANDA respond well to intravenous or subcutaneous immunoglobulins administration.[6] Immunomodulatory therapy with Rituximab, which is often used as second-line treatment, has also been successful.[1]

There is a lack of evidence in the literature regarding possible rehabilitation approaches for patients with CANDA.

Materials and Methods

Case Report

We describe the case of a 45-year-old male patient who developed diplopia, buccal and limb paresthesias, "stocking-like" hypoesthesia and dysto-proximal hyposthenia in the LLs right after an emergency appendectomy (October 2018). Diagnostic investigations revealed positivity to anti-GD1b IgM antibodies: a diagnosis of CANDA was made.

The most recent electromyography of the LLs was performed on June 19, 2019. The neurologist concluded: "The neurophysiological findings are compatible with demyelinating sensorimotor polyneuropathy with an axonal component. Clinically, the patient showed predominantly proximal lower limb strength deficits, with F-wave prolongation over 130% of the laboratory-predicted normal range". Ultrasound nerve studies were not conducted. Since then, the patient has been treated with monthly courses of intravenous immunoglobulin administration (IV Ig, 180 g in 4 days) and oral steroid

therapy. In March 2020, he was treated with Rituximab (375 mg/m^2), with little benefit. He then resumed IV Ig administration every 4 weeks, prior undergoing regular neurological checkups. As for the patient's motor skills, he was able to walk short stretches with the aid of a walker, whereas a wheelchair was needed to cover longer distances. He managed to take a few steps without a walking aid only if supported by a caregiver. The patient reported a relevant motor performance improvement and muscle strength recovery right after the first few days of every IV Ig administration, while describing a decreasing motor function over the next weeks. The resulting consistent pattern made it necessary to start new cycles of IV Ig therapy every other 4 weeks. In order to reduce the frequency of therapy cycles and to maintain motor skills improvements over time, the patient underwent 4 plasmapheresis sessions in a row (October 2022); however, it was immediately reported a sudden worsening of clinical and motor picture, observing severe fatigability and loss of strength in the LLs.

On account of the worsened motor skills and limited functional ability to perform activities of daily living, the patient was initiated to a new IV Ig cycle and subsequently hospitalized to perform intensive rehabilitation.

Assessment

After signing an informed consent, the patient was evaluated by a single practitioner (physiatrist) at the beginning of hospitalization (T0), at the end of a second cycle with IV Ig (T1, at 20 days from T0), and at discharge (T2, at 35 days from T0). Medical assessment was completed by administration of the following scales, in the form of paper questionnaires filled out by the doctor:

1. Barthel Index (BI), an ordinal scale which measures a person's ability to complete Activities of Daily Living (ADL);[7]
2. Functional Independence Measure (FIM) scale, an assessment tool that aims to evaluate the functional status of patients throughout the rehabilitation process; for our patient's evaluation we focused on the motor functionality (self-care, sphincter control, transfers, locomotion) as he wasn't affected by neither cognitive nor communicative deficits;[8]
3. Four limb strength assessment by manual muscle testing using the Medical Research Council (MRC) scale;[9]
4. Short Form-12 Health Status Questionnaire (specifically the Mental Component Score, MCS-12);[10]
5. Modified Toronto Clinical Neuropathy Score (mTCNS):[11] originally designated for the evaluation of diabetic neuropathy, we used it to assess characterize neuropathic symptoms in the absence of specific scales for CANDA;
6. Neurological physical examination and graphic representation of the distribution of paresthesias and deficits in superficial tactile and pain sensitivity.

Training protocol

The patient underwent intensive inpatient rehabilitation treatment involving two individual sessions per day (one in the morning and one in the afternoon) of approximately 90 minutes each for 5 days a week for the entire duration of the hospitalization. The trainings included physical exercises, executed with the help of qualified physiotherapists; rehabilitation devices (such as cyclette) were also used. No biofeedback stimulators were used. Goals for rehabilitation were muscle strengthening of the LLs, proprioceptive stimulation and reeducation, improvement of autonomy in verticalization, balance and gait training with aids. After the first rapid deterioration of the motor picture (T0 to T1), the patient's performance was more affected by LLs hyposthenia than by balance problems (despite ataxia being one of the main clinical features of CANDA). Therefore, the rehabilitation treatment -especially in the early stages of the hospitalization- focused on strengthening the LLs muscles. Specifically, muscle strengthening exercises focused on hip flexion against gravity, open-chain resistance quadriceps eccentric exercises, ankle flexion-extension against resistance and trunk muscle enhancement to enable better postural control. Balance keeping while standing was trained with repetitions of stand-up and sit-down sequences, which the patient was able to execute exclusively thanks to the anterior support of an antibrachial walker. Gait training was performed with the aid of an antibrachial walker or on parallel bars. The patient always needed the support of a trained physiotherapist. The performed exercises were progressively adapted to the improvements of the patient's motor performance (especially after the IV Ig cycle administered during hospitalization), through an increased level of difficulty of the exercises, number of repetitions, and reduction of cool-down breaks duration.

Results

During hospitalization it was registered a moderate improvement of strength during the flexion-extension movements of the major joint districts of the LLs (MRC Sum score at the LLs: 19/30 at T0, 22/30 at T1, 23/30 at T2), especially on the proximal side (Figure 1). On the contrary, we did not observe a significant change of hypoesthesia, anesthesia and "stocking-like" tingling paresthesias detected on both limbs at time of admission. The pain sensitivity deficit detected at T0 regressed at T1 (and maintained at T2) (Figure 2). Furthermore, progressive improvements were recorded both in patient's motor performance (FIM motor part: 72 at T0, 76 at T1 and 79 at T2) and in his level of autonomy in activities of daily living (BI: 50/100 at T0 , 60/100 at T1 and 75/100 at T2). The patient was compliant and motivated by the proposed rehabilitation treatment.

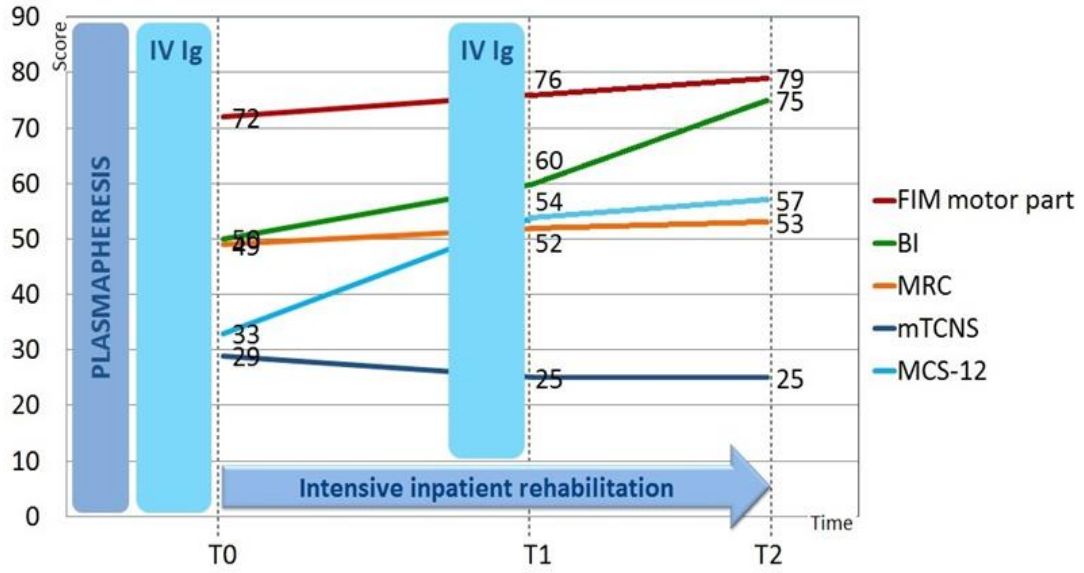

Fig 1. *Graphical representation of the results (FIM motor part, Barthel Index, MRC Sum score of the LLs, mTCNS and MCS-12) at T0, T1 and T2.*

A significantly enhanced mood was noted. He also showed to be more and more confident about the possibility of concrete recovery and quality of life improvements (MCS-12: 33 at T0, 54 at T1 and 57 at T2). At the moment of pre-discharge evaluation (T2), the patient had already showed a slight decrease of motor performance and strength compared with all of the previous days noted improvements: the maximum synergistic effect between IV Ig therapy and rehabilitation was reached about 3 weeks after the beginning of the last cycle of IV Ig admission.

After being discharged, the patient underwent the next cycle of therapy 5 weeks after the previous one and continued rehabilitation as an outpatient to consolidate all of the progress he made during hospitalization in a different Rehabilitation Hospital, near his house. He had then gradually resumed his daily activities. He no longer performed plasmapheresis. He's been keeping a frequency of IV Ig cycles administration every 5 weeks while his neurologists are evaluating another attempt at Rituximab treatment.

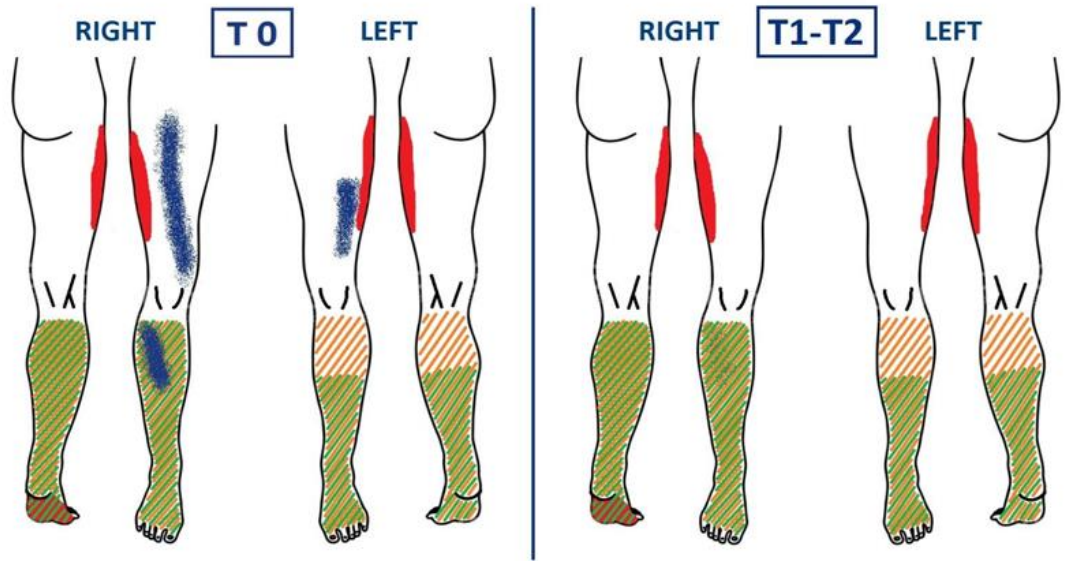

Fig 2. *Graphical representation of the results (FIM motor part, Barthel Index, MRC Sum score of the LLs, mTCNS and MCS-12) at T0, T1 and T2.*

Discussion

In the described case, the combination of IV Ig therapy and intensive inpatient rehabilitation is associated with an improvement of lower limb muscle strength and global motor performance, which correlates with a relevant improvement of the patient's autonomy to perform activities of daily living and quality of life.
It also made possible to reduce the frequency of treatments with IV Ig, both decreasing the number of annual hospital accesses and potentially lowering the cost of treatment borne by the National Health System.
In addition to the exercise itself, we believe that the hospital's secured environment and the help of trained physiotherapists allowed the patient to completely focus on his rehabilitation and were, therefore, co-responsible factors of his improvements.
In this case, the patient's medical history shows that treatment of CANDA with plasmapheresis was associated with a worsening of clinical picture and reduced motor performance: if confirmed by other evidence, this treatment approach would therefore be reconsidered.
We also discuss potential strategies to implement the patient's rehabilitation. Muscle strengthening exercises of the LLs could have been combined with electrical stimulation sessions targeting the impaired muscles,[12] however a recent EMG evaluation is usually recommended before assessing electrical stimulation parameters for denervated/partially denervated muscles, and in this case was not available.
The use of advanced rehabilitation technologies for balance and gait training (e.g. wearable sensors and an interactive user interface for real-time visual feedback) would also have been useful but unfortunately the rehabilitation facility where the patient was admitted did not have such devices.[13]
This is the first case in literature reporting the combined effect of rehabilitation treatment and medical therapy in CANDA neuropathy. To confirm the effectiveness of this approach, it will be necessary to apply it to as many patients as possible (compatible with the low prevalence of the disease). Also, we suggest the possibility to design a specific evaluation scale to assess and monitor CANDA neuropathy severity and progression of symptoms.

List of acronyms

ADL - Activities of Daily Living
BI - Barthel Index
CANDA - Chronic Ataxic Neuropathy with anti-Disialosyl IgM Antibodies
EMG – electro myography
FIM - Functional Independence Measure
IV Ig - intravenous immunoglobulin administration
LLs - lower limbs
MCS-12 - Mental Component Score
MRC - Medical Research Council
mTCNS - Modified Toronto Clinical Neuropathy Score

Contributions of Authors

GB performed functional evaluations, contributed to data analysis and interpreted the results. AM set the rehabilitation goals and designed the training protocol. AM, AP and LO contributed to interpretation of data and supervised the manuscript. All authors read and approved the final edited version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interests, since they did not receive any funding for the present research.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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