Annals of Clinical and Medical Case Reports

Case Report

ISSN 2639-8109 | Volume 13

Axonal Polyneuropathy with Anti-Caspr1 Igg1 Paranodal Antibodies

Sun X, Hou Y, Zhang Z, Jin F and Zhu J*

Department of Neurology, The third central hospital of Tianjin, Tianjin, China

***Corresponding author:**

Ju Zhu,

Department of Neurology, The third central hospital of Tianjin, Tianjin, China

Received: 14 Jan 2024

Accepted: 05 Mar 2024

Published: 12 Mar 2024

J Short Name: ACMCR

Keywords:

Anti-Caspr1 antibody; IgG1; Axon; Case report; Paranodopathy

Citation:

Zhu J, Axonal Polyneuropathy with Anti-Caspr1 Igg1 Paranodal Antibodies. Ann Clin Med Case Rep. 2024; V13(5): 1-6

1. Abstract

1.1. Objectives: The main electrophysiological manifestation of autoimmune paranodopathy with anti-contactin-associated protein 1 (Caspr1) positive reported previously was demyelination, with or without axonal involvement. Here, we reported a patient with anti-Caspr1 IgG1 positive who had severe axonal involvement accompanied less evidence of demyelination.

1.2. Case Presentation: We reported a 65-year-old man, who had weakness in the distal limbs, without pain or tremor. Anti-Caspr1 antibody was detected and shown to be of IgG1 subclass by Cell-based assays (CBA). At the onset of disease, electrophysiological test indicated axonal involvement, even at the upper limbs with no symptoms or signs. After follow-up for 2 years, the clinical symptoms and electrophysiologic results of the patient continued to deteriorate. And he had poor or partial response to corticosteroids, immunoglobulin, plasma exchange or even rituximab.

1.3. Conclusion: The refractory patient with anti-Caspr1 IgG1 antibodies was characterized by axonal involvement. These distinguishing manifestation from other anti-Caspr1 paranodopathies may be associated with different IgG subclasses.

2. Introduction

In the last decade, the exploration of antibodies against the nodes of Ranviers has brought into a new concept of autoantibodies-mediated neuropathies which has distinguished clinical presentation and pathogenic mechanism from typical chronic inflammatory demyelinating polyneuropathy (CIDP) [1]. The European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) diagnostic and therapeutic CIDP guidelines, published in 2021, recommended this disorder as an independent new diagnostic category from the CIDP variant classification [2].

Contactin-associated protein 1 (Caspr1) is an important adhesion molecule located in paranodal regions [3]. It participates in the formation of a septate-like junctions with neurofascin-155 (NF155), and contactin-1 (CNTN1), which anchors the myelin sheath to axon and preserves the segregation of the potassium channels of the juxtaparanodal region and the sodium channels of the nodal region [3, 4]. Disruption of this organization can lead to abnormalities of saltatory conduction in myelinated fibers.

Paranodopathies with anti-Caspr1 antibodies represent a rare autoimmune neuropathy, the frequency reported previously was only 0.5%-2.9% among patients with CIDP [4-6]. IgG4 was detected as the most prevalent IgG subclass [6-8]. The electrophysiological evidences of demyelination, such as decreased nerve conduction velocity (CV), prolonged distal latency of motor nerve and F-waves latency, were the typical findings among these patients confirmed in previous researches [6, 7, 9, 10], however, segmental de-remyelination was absent in nerve biopsy studies. Moreover, the clinical features, electrophysiological manifestation and pathophysiological mechanisms among patients with non-IgG4 subclasses remained inadequately.

We report a case of axonal polyneuropathy with anti-Caspr1 IgG1 paranodal antibodies. We describe the longitudinal changes of clinical symptoms, serial electrophysiological findings and response to different therapies of this patient for expanding understanding of the spectrum of anti-Caspr1 antibodies-associated paranodopathies.

3. Materials and Methods

3.1. Case Presentation

The patient was a 65-year-old male, who developed progressive weakness of distal lower limbs over the past 2 months (July 2020). There were no symptoms of cranial nerve or upper limbs. Neurological examination of this patient at admission revealed normal cranial nerve and upper limbs function, motor weakness (4/5) affecting the distal lower extremities, and decreased superficial sensation in a stocking distribution limited to the level of the feet. His Overall Neuropathy Limitations Scale (ONLS) score was 1. Nerve conduction studies of lower limbs (Table 1) showed features of motor axonal neuropathy including decreased compound muscle action potential (CMAP), normal CV, distal motor latency (DML) and sensory conduction. Electromyography (EMG) revealed spontaneous activity and regeneration potentials (increased amplitudes, broadened durations) in both Tibialis anterior. No clinical involvement of the upper limbs, but the motor nerve conduction studies (NCS) demonstrated decreased CMAP of the median nerve, with normal CV, and denervation in Abd pollicis brevis (APB) on EMG (Table 1). There were obviously diminished F-waves persistences of median nerve and no tibial F-waves were recorded. The protein level in the cerebrospinal fluid (CSF) was elevated at 1.46 g/L. The results of other parameters of CSF tests, routine blood tests, and biochemical tests were negative. Tests for paraneoplastic antibodies and anti-ganglioside antibodies were negative in both of the serum and CSF.

Table 1: Results of the serial electrophysiological examinations.

Nerve studies	2020.07		2020.1		2022.08		2023.04		Normal values
	left	right	left	right	left	right	left	right	
Median nerve									
DL (ms)	3.1	3.2	3.5	3.7	4	3.9	3.8	3.7	≤4.1
MCV (m/s)	63.9	60.4	52.3	54.6	51.6	54.1	56	51	≥51.0
CMAP(mV)	3.5↓	5.8↓	1.9↓	5.2↓	1.6↓	3.1↓	1.3↓	2.8↓	≥7.0
F-wave latency (ms)	28.9	27.2	NR	25.1	NR	NR	NR	NR	≤30
F-wave frequenc(%)	20	60	NR	60	NR	NR	NR	NR	≥80
SCV (m/s)	55.8	52.4	54.8	48.4	46.1	50.1	53.3	52.4	≥41.8
SNAP(μV)	30	28.6	23.1	26.5	13.3	13.8	12.9	15.2	≥12.7
Ulnar nerve									
DL (ms)	2.4	2.6	2.7	2.9	2.9	3.3	2.9	3.4	≤3.8
MCV (m/s)	65	64.7	64.2	61.5	58.5	56.3	57.2	56.4	≥56.0
CMAP(mV)	10.6	11.4	8.2	9.1	5.5↓	6.3 ↓	2.9 ↓	3.7 ↓	≥7.0
F-wave latency (ms)	ND	25.5	ND	27	ND	24.5	NR	27.6	≤30
F-wave frequenc(%)	ND	100	ND	100	ND	55	NR	35	≥80
SCV (m/s)	54.6	55.1	51.7	49.2	53.1	60	50	50	≥44.2
SNAP(μV)	10.4	13.6	9.3	12.1	7.2	7.9	7.2	10.7	≥6.9
Tibial nerve									
DL (ms)	3.7	3	NR	NR	NR	NR	NR	NR	≤4
MCV (m/s)	43.3	41.2	NR	NR	NR	NR	NR	NR	≥40.5
CMAP(mV)	0.27↓	0.13↓	NR	NR	NR	NR	NR	NR	≥5.1
F-wave latency (ms)	ND	NR	ND	NR	ND	NR	NR	NR	≤35
F-wave frequenc(%)	ND	NR	ND	NR	ND	NR	NR	NR	≥75
SCV (m/s)	43.8	44	41	43.4	NR	NR	NR	NR	≥35.1
SNAP(μV)	1.3	1.1	1.3	1.6	NR	NR	NR	NR	≥0.4
Peroneus nerve									
MCV (m/s) Ankle-EDB	NR	NR	NR	NR	NR	NR	NR	NR	≥3.6
CMAP(mV) Ankle-EDB	NR	NR	NR	NR	NR	NR	NR	NR	≥3.6
CMAP(mV) Fib.Head-Ankle	2.6↓	2.0↓	1.2↓	1.1↓	NR	NR	NR	NR	≥4.8
SCV (m/s)	50.8	47.6	58.7	51.5	NR	NR	NR	NR	≥46.5
SNAP(μV)	0.8	0.8	1.4	1.4	NR	NR	NR	NR	≥0.8

Abbreviations: CMAP, compound muscle action potential; DL, distal latency; EDB, extensor digitorum brevis; L, left; MCV, motor conduction velocity; ND, not detected; NR, not recordable; R, right; SCV, sensory conduction velocity; SNAP, sensory nerve action potential.

3.2. Cell-based assays for antibodies against NF155, CNTN1, and Caspr1

Human embryonic kidney cells were transfected with plasmids of human NF155, CNTN1, or Caspr1(NM_003632.3), fixed in paraformaldehyde at 4℃ for 20 minutes, and incubated in 5% BSA for 45 min at RT (room temperature). Then, the cells were incubated with patient's sera (dilution 1:10) or patient' s CSF (dilution 1:1) for 1h. After washing, cells were incubated with TRITC-conjugated goat anti-human IgG antibodies (1:100, Thermo Fisher) for 45min at 37°C in the dark. Images were acquired using a fluorescence microscope (Olympus).

3.3. Determination of IgG Subclasses

The caspr-1 antibody was detected using fixed cell-based assay (CBA) kit (Tianjin New Terrain Biotechnology, Inc, Tianjin, China) according to manufacturer's instructions. Briefly, in the fixed CBA of Caspr-1 antibody, 293 T cells were transfected with plasmid expressing Green Fluorescent Protein (GFP) labeled human caspr-1 in 96-well plates. At 24h later, the transfected 293 T cells were fixed with 4% polyformaldehyde. For immunostaining, the plate with 293 T cells expressing Caspr-1 was rinsed twice with PBS and incubated at 37C for 30 minutes in a blocking buffer containing 10% goat serum. Then 80ul of sample diluent and the negative/positive control sample were added to wells. The plate was then shaken for three to five minutes and incubated at 37 degrees Celsius for one hour. The plate was then rinsed three times with PBSIgG1-4 secondary incubated with 80uL anti-human antibody at 37 degrees Celsius (avoid light) for 30minutes, then washed three times. And 150ul PBS was added to each well to cover the cells prior to fluorescence microscopy imaging. The antibody titer was determined by diluting the serum sample 1:10, 1:32, and 1:100.

4. Results

4.1. Detection of Autoantibodies against Paranodal Proteins

Analysis for autoantibodies against node of Ranvier proteins in his serum and CSF samples revealed anti-Caspr1 antibodies positive in the serum (1:10) and CSF (1:3.2). There were negative findings for anti-NF155, and anti-CNTN1 antibodies (Figure 1).

4.2. Detection of Isotype of Caspr1

Anti-Caspr1 IgG1 antibodies were positive in the serum of the patient in our study (Figure 2). No immunoreactivity of IgG2, IgG3 and IgG4 was detectable.

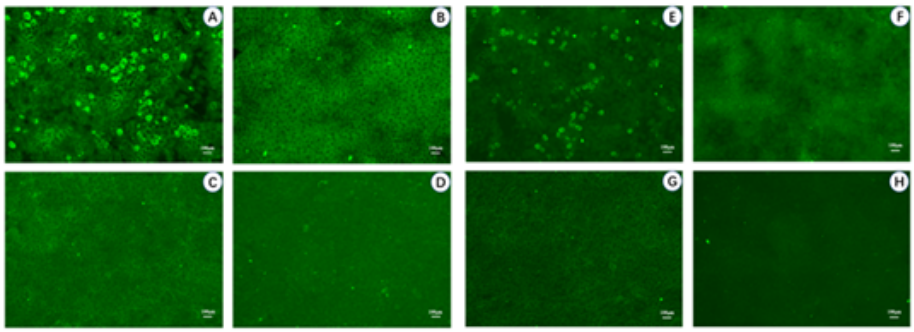

Figure 1: Detection of anti-NF155, CNTN1 and Caspr1 antibodies in serum and cerebrospinal fluid (scale bar:100μm)
Cell-based assays revealed a positive finding for the anti-Caspr1 antibody in serum (1:10) (A), and the negative control of the anti-Caspr1 antibody(B). The (C, D) show the negative finding for the anti-CNTN1 and anti-NF155 antibody in serum.
The E shows a positive finding for the anti-Caspr1 antibody in CSF (1:3.2), while panel F shows the negative control of the anti-Caspr1 antibody. The (G, H) shows the negative finding for the anti-CNTN1 and anti-NF155 antibody in CSF.

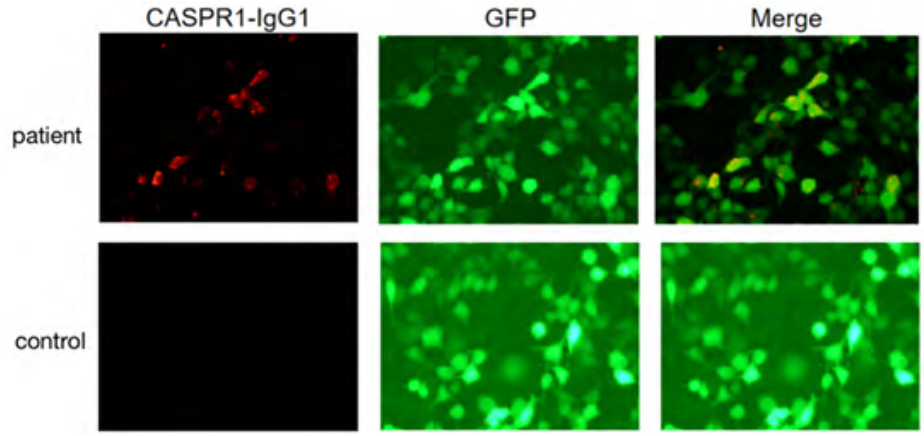

Figure 2: Detection of Caspr-1 antibody IgG subset.
HEK-293T cells express Caspr-1 and Green Fluorescent Protein (GFP) were used as antibody harboring cells (green color). Plasma from both control and patient was detected simultaneously. Antibodies against IgG1-4 were utilized as secondary antibodies to detect the subset of IgG. The combination of caspr-1 and the patient's IgG1 antibody at a dilution ratio of 1:100 is depicted in a merge of two images (orange color).

4.3. Therapy and follow-up

Based on the results described above, the case was diagnosed as anti-Caspr1 IgG1 antibodies-positive paranodopathy. The patient was administered methylprednisolone (1g/day), but the therapy was interrupted at the third day because of deterioration of weakness in his proximal lower limbs. Then, he received plasma exchange for 3 times and had slight improvement of motor weakness at lower limbs for several weeks (4+/5) (Table 2).

The distal weakness slightly aggravated in the next month (ONLS score:2), thus the patient was admitted again in Oct 2020. The protein level in the CSF elevated to 1.81 g/L. Anti-Caspr1 antibodies were re-tested and confirmed positive in serum and CSF via CBA testing. No improvements were observed after treatment with IVIG (0.4mg/kg/day for 5 days).

Symptoms were continuously progressive. The patient was admitted in our hospital presented foot-drop, steppage gait and mild hands clumsiness in July 2022. Neurological examination revealed normal cranial nerve function, weakness and atrophy affecting the distal extremities (lower 2-/5, upper 5-/5), and decreased distal superficial sensation presented glove-stocking distribution (ONLS score: 6). NCS examinations (table1) showed decreased CMAP of the median and ulnar nerve, with normal CV and sensory conduction. There was no response to stimulation in motor and sensory conduction of the lower limbs, with absent F-waves. Magnetic resonance imaging (MRI) neurography showed mild symmetric hypertrophy in the cervical plexus, without abnormality in the lumbosacral plexus (Figure 3). The patients showed no improvement with rituximab (100 mg/d for 3 days).

The patient walked for shorter distances with crutches and developed having difficulty with using spoon in April 2023 (ONLS score:7) (Table 2). NCS examination results were similar to those in 2022 (Table 1).

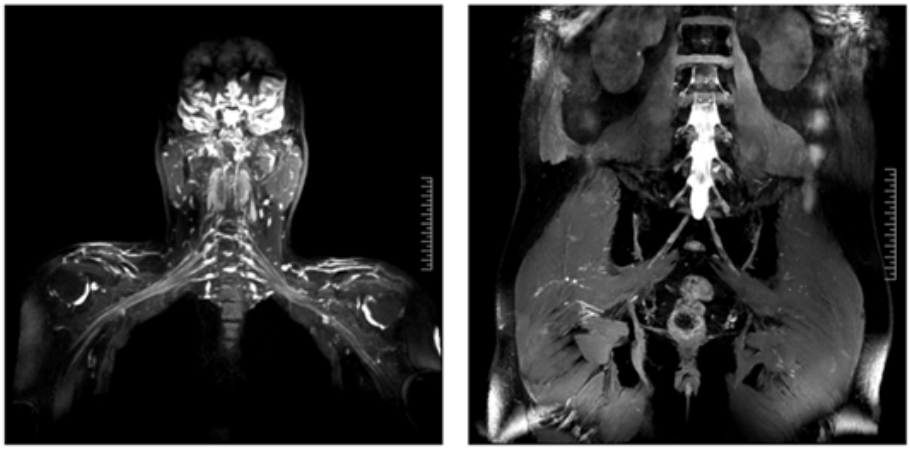

Figure 3: MRI neurography imaging of cervical and lumbosacral plexuses.
The patient showed mild symmetric hypertrophy in the cervical plexus. No abnormality was found in the lumbosacral plexus.

Table 2: Course of disease in the patient.

Date of assessment	2020.07	2020.1	2022.08	2023.04
MRC grade	Upper limbs: 5; lower limbs: proximal 5, distal 4	Upper limbs: 5; lower limbs: proximal 5, distal 3	Upper limbs: proximal 5, distal 5-; lower limbs: proximal 5-, distal 2-	Upper limbs: proximal 5, distal 4; lower limbs: proximal 5-, distal 0
ONLS score	1	2	6	7
Ambulation	Without aid	Without aid	Crutches	crutches for shorter distances
Hypesthesia	Feet	below the knee	below the hip joint and hands	below the hip joint and hands
CSF	protein 1.42g/L	protein 1.81g/L	Not done	Not done
Caspr1	positive	positive	positive	
Treatment	PE:partial effective Steroids:intolerant	IVIG:ineffective	Rituximab: ineffective	

5. Discussion

Patients with anti-Caspr1 antibodies represent a rare subset of paranodopathy patients. These patients are characterized by subacute onset, motor weakness, sensory ataxia, neuropathic pain, cranial nerve palsies, and respiratory failure [6, 7, 9, 10]. The pathogenic antibodies detected among these patients are usually of the IgG4 subclass [6, 7, 11]. Whereas the clinical manifestations in this case with anti-Caspr1 IgG1 antibodies was limited to distal weakness, especially in the lower extremities, with no pain or cranial involvement. Subclasses of antibodies may be the reason for the clinical disparities. Meanwhile, this patient showed increased CSF protein level and mild symmetric hypertrophy in the cervical plexus on MRI neurography. These findings suggested the presence of inflammatory reactions and blood-nerve barrier disruption in the nerve plexus, such that antibodies may pass through these sites to travel to nodes of Ranvier [9].

The serial electrophysiological tests of this patient indicated deterioration of disease. At the onset (2020), the reduced CMAP amplitude at the distal extremities, and neurogenic impairments on EMG indicated axonal involvement. After 2 years, the reduced and non-recordable CMAP and SNAP indicated the axonal degeneration. These electrophysiological results were inconsistent with demyelinating-like manifestation, the electrophysiological feature of the patients with anti-Caspr1 antibodies reported previously [6, 7, 9, 10]. Besides, the reduced distal CMAP amplitude may be due to reversible conduction failure (RCF), which is considered be related to impairment of the nodal axolemma [12, 13]. Serial motor conduction studies of RCF revealed the conductions could be reversed within several weeks. In a special case of RCF, the conductions were within the normal range on Day 8, CB presented (43% reduction of proximal CMAP) on Day 39, and nerve conductions were almost in the normal range on Day 332 [14]. However, in this case, after more than 2 years of follow-up, we did not find any reversal of clinical symptoms or electrophysiological results. Thus, the current results lacked evidence to support RCF.

Whereas the nerve biopsies reveal axonal loss without signs of de-remyelination [7, 15, 16]. Semi-thin sections of patients with anti-CNTN1 antibodies showed axonal loss and degeneration of nerve fibers [17], supporting the idea that the axonal loss among paranodopathies caused by disruption of paranodal architecture that do not follow the classical demyelinating neuropathies. Sural nerve biopsy of Doppler's patient with anti-Caspr1 antibodies revealed severe axonal loss, numerous degenerating axons, but only a few thinly myelinated fibres and no onion bulbs [6]. The results from biopsy studied before showing features of axonal damage corroborate the electrophysiological results of this patient in some extent.

The reason of axonal diminishment may be associated with microstructural disruption. Caspr1 binds to the paranodal/juxtaparanodal cytoskeletal scaffolding protein Band 4.1B to ensure stable interactions between the membrane proteins and axonal cytoskeleton. Anti-Caspr1 antibody compromises these domains and clustering of juxtaparanodal Kv channels, inducing axon degeneration [18]. Furthermore, pathological changes in peripheral axonal morphology and their electrophysiological properties are often accompanied by neuromuscular junction (NMJ) dysfunction, leading to impaired synaptic transmission and eventually NMJ denervation and degeneration [19, 20]. "Dying back" neurological disorders are characterized by initial degeneration of the distal axons, with the presynaptic terminal being the most vulnerable part of this process [19]. Julia Saifetiarova and colleagues showed that mutants of Caspr1 and or Caspr2 leads to pre- and postsynaptic pathological changes at NMJs and their denervation [18]. These neuromuscular deficits over time lead to muscle atrophy or muscle fiber degeneration.

Previous studies found that two of three patients who received IVIG had a partial response; three of four patients who received steroids had a partial response; one of the three patients who received plasma exchange had a good response, and two patients receiving immune suppressors had a good effect [7, 9, 21]. In the present case, there was poor response to IVIG, corticosteroids and rituximab, while plasma exchange showed partial efficacy. We suppose the disparities of treatment response may be associated with the subclasses of antibodies. Up to now, anti-Caspr1 IgG1 antibodies-associated paranodopathies were rarely reported, and pathogenic mechanism has not been elucidated.

Our report has limitations. Firstly, we did not obtain the nerve biopsy results of this patient. Secondly, we did not identify the IgG subclasses of this patient every follow-up visit. We will conduct a nerve biopsy and measuring IgG subclasses in further follow-up for exploring effective treatment options.

In conclusion, we describe a refractory case of anti-Caspr1 IgG1 positive paranodopathy with severe axonal involvement. The case highlights the importance of antibody detection and subclassification for the diagnosis and treatment of autoimmune nodo- and paranodopathies.

References

1. Broers M C, Bunschoten C, Nieboer D, Lingsma H F, Jacobs B C. Incidence and Prevalence of Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Systematic Review and Meta-Analysis. Neuroepidemiology. 2019; 52(3-4): 161-72.
2. Van den Bergh PYK, van Doorn PA, Hadden RDM, Avau B, Vankrunkelsven P, Allen JA, et al. European Academy of Neurology/ Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force-Second revision. Eur J Neurol. 2021; 28(11): 3556-83.
3. Vural A, Doppler K, Meinl E. Autoantibodies Against the Node of Ranvier in Seropositive Chronic Inflammatory Demyelinating Polyneuropathy: Diagnostic, Pathogenic, and Therapeutic Relevance. Front Immunol. 2018; 9: 1029.
4. Delmont E, Brodovitch A, Kouton L, Allou T, Beltran S, Brisset M, et al. Antibodies against the node of Ranvier: a real-life evaluation of incidence, clinical features and response to treatment based on a prospective analysis of 1500 sera. J Neurol. 2020; 267(12): 3664-72.
5. Liberatore G, De Lorenzo A, Giannotta C, Manganelli F, Filosto M, Cosentino G, et al. Frequency and clinical correlates of anti-nerve antibodies in a large population of CIDP patients included in the Italian database. Neurol Sci. 2022; 43(6): 3939-47.
6. Doppler K, Appeltshauser L, Villmann C, Martin C, Peles E, Krämer H H, et al. Auto-antibodies to contactin-associated protein 1 (Caspr) in two patients with painful inflammatory neuropathy. Brain. 2016; 139(Pt 10): 2617-30.
7. Cortese A, Lombardi R, Briani C, Callegari I, Benedetti L, Manganelli F, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2020; 7(1).
8. Pascual-Goñi E, Fehmi J, Lleixà C, Martín-Aguilar L, Devaux J, Höftberger R, et al. Antibodies to the Caspr1/contactin-1 complex in chronic inflammatory demyelinating polyradiculoneuropathy. Brain. 2021; 144(4): 1183-96.
9. Li C, Zheng H, Yuan C, Li Y, Hu Y, Jiang H. Two CIDP Variants Patients With Anti-Caspr1 Antibodies in South China. Front Immunol. 2022; 13: 844036.
10. Liu L, Chen J, Zhang Y, Wu J, Hu J, Lin Z. Case report: Immunoadsorption therapy for anti-caspr1 antibody-associated nodopathy. Front Immunol. 2022; 13: 986018.
11. Uncini A, Mathis S, Vallat J M. New classification of autoimmune neuropathies based on target antigens and involved domains of myelinated fibres. J Neurol Neurosurg Psychiatry. 2022; 93(1): 57-67.
12. Uncini A, Kuwabara S. Nodopathies of the peripheral nerve: an emerging concept. J Neurol Neurosurg Psychiatry. 2015; 86(11): 1186-95.
13. Umapathi T, Tan E Y, Kokubun N, Verma K, Yuki N. Non-demyelinating, reversible conduction failure in Fisher syndrome and related disorders. J Neurol Neurosurg Psychiatry. 2012; 83(9): 941-8.
14. Uncini A, Susuki K, Yuki N. Nodo-paranodopathy: beyond the demyelinating and axonal classification in anti-ganglioside antibody-mediated neuropathies. Clin Neurophysiol. 2013; 124(10): 1928-34.
15. Gupta P, Mirman I, Shahar S, Dubey D. Growing Spectrum of Autoimmune Nodopathies. Curr Neurol Neurosci Rep. 2023; 23(5): 201-12.
16. Appeltshauser L, Brunder A M, Heinius A, Körtvélyessy P, Wandinger K P, Junker R, et al. Antiparanodal antibodies and IgG subclasses in acute autoimmune neuropathy. Neurol Neuroimmunol Neuroinflamm. 2020; 7(5).
17. Doppler K, Appeltshauser L, Wilhelmi K, Villmann C, Dib-Hajj S D, Waxman S G, et al. Destruction of paranodal architecture in inflammatory neuropathy with anti-contactin-1 autoantibodies. J Neurol Neurosurg Psychiatry. 2015; 86(7): 720-8.
18. Saifetiarova J, Liu X, Taylor A M, Li J, Bhat M A. Axonal domain disorganization in Caspr1 and Caspr2 mutant myelinated axons affects neuromuscular junction integrity, leading to muscle atrophy. J Neurosci Res. 2017; 95(7): 1373-90.
19. Maggs A M, Huxley C, Hughes S M. Nerve-dependent changes in skeletal muscle myosin heavy chain after experimental denervation and cross-reinnervation and in a demyelinating mouse model of Charcot-Marie-Tooth disease type 1A. Muscle Nerve. 2008; 38(6): 1572-84.
20. Pollari E, Goldsteins G, Bart G, Koistinaho J, Giniatullin R. The role of oxidative stress in degeneration of the neuromuscular junction in amyotrophic lateral sclerosis. Front Cell Neurosci. 2014; 8: 131.
21. Tang L, Huang Q, Qin Z, Tang X. Distinguish CIDP with autoantibody from that without autoantibody: pathogenesis, histopathology, and clinical features. J Neurol. 2021; 268(8): 2757-68.