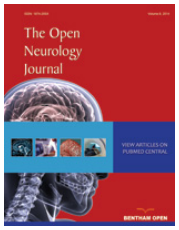

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RESEARCH ARTICLE

Epidemiology and Clinical Course of Chronic Autoimmune Neuropathies During the SARS-CoV-2 Pandemic in Latvia

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Abstract:

Background:

Chronic autoimmune neuropathies are a group of rare neurological disorders caused by the immune response to autoantigens in the peripheral nervous system.

Objective:

This study aimed to report epidemiological data in Latvia on the most common chronic autoimmune neuropathies and evaluate SARS-CoV-2 infections or vaccinations' impact on our patient's clinical course of the disease.

Methods:

A single-center observational study was performed, which included all patients diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) in Latvia since 2015. Prevalence and incidence were calculated by using population data from the corresponding time of the Central Statistics Bureau of Latvia. Detailed clinical evaluation and re-assessment of diagnostic criteria were performed in the whole study group. All patients underwent telephone interviews regarding their SARS-CoV-2 vaccination or infection status.

Results:

This study included 23 CIDP and 8 MMN patients. The point prevalence and incidence of CIDP were 1.21 per 100 000 people and 1.16 per 100 000 people, respectively. The point prevalence and incidence of MMN were 0.42 per 100 000 individuals and 0.40 per 100 000 individuals, respectively. Most of the patients involved in this study (90%, n=28) with CIDP or MMN were vaccinated against SARS-CoV-2 infection, and none of the patients experienced fluctuations or relapse regarding autoimmune polyneuropathy.

Conclusion:

The incidence and prevalence of CIDP and MMN in Latvia are similar to previously reported European studies. In our study group, vaccination against SARS-CoV-2 was safe and did not negatively affect the clinical course of CIDP and MMN patients.

Keywords: Autoimmune neuropathies, Chronic inflammatory demyelinating polyradiculoneuropathy, Multifocal motor neuropathy, Epidemiology, SARS-CoV-2, Vaccination.

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1. INTRODUCTION

Autoimmune neuropathies are a group of rare neurological disorders caused by immune responses to autoantigens in the peripheral nervous system (PNS). Autoimmune neuropathies are classified as acute, including Guillain-Barré syndrome and its variants, and chronic: chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants and multifocal motor neuropathy (MMN) [1].

While autoimmune neuropathies are rare, their exact prevalence and incidence are largely unknown as extensive

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reports with systematically collected data on epidemiology by country are scarce [1, 2]. Reported incidence and prevalence vary by disorder and type of neuropathy and by study or country. CIDP is the most common chronic autoimmune neuropathy, with a point prevalence ranging from 2.7-7.7 per 100 000 in Europe [2]. However, the prevalence has been reported as low as 0.8 in Japan and as high as 8.9 in the US. Data regarding MMN are even more limited. The prevalence of MMN has been reported as 0.29-0.6 per 100 000 individuals [1].

The reported variability in epidemiological data in different geographical regions is most probably multifactorial. Likely, patients are often misdiagnosed due to the clinical similarities of other autoimmune, as well as hereditary neuropathies or under-recognised due to the diagnosis' complexity and resources needed for appropriate diagnostics [1, 2].

While vaccination against SARS-CoV-2 is recommended for patients with chronic autoimmune neuropathy, there are currently limited data regarding the immunization status of this group of patients, as well as the potential effect of vaccination or infection on the clinical course of the disease [3].

This study aimed to report epidemiological data in Latvia on the most common chronic autoimmune neuropathies, assess our patients' status with SARS-CoV-2 infection and vaccination, and evaluate their impact on the clinical course.

2. MATERIALS AND METHODS

This study included 31 patients diagnosed with the most common chronic autoimmune neuropathies - 23 CIDP and 8 MMN. Our cohort represents all patients diagnosed with CIDP and MMN in Latvia since 2015. All patients with suspected and/or confirmed chronic autoimmune neuropathies are referred to our tertiary center for diagnosis and treatment, the only center providing treatment for these disorders. All our study group patients have had regular follow-up visits every 3 months since 2019. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008 and approved by the Central Medical Ethics Committee of Latvia approval Nr.3/18-03-21. Informed consent was obtained from all subjects involved in the study.

CIDP patients were originally diagnosed using the criteria developed by EFNS/PNS in 2010. Following the updated 2021 EFNS/PNS diagnostic criteria, they were reevaluated by a neuromuscular/neuro-immune disorders expert [4]. The reevaluation process did not affect the number of patients involved in this study. MMN patients were diagnosed using criteria the EFNS/PNS updated in 2010 [5]. Scales and tools used for clinical assessment - Medical Research Council (MRC) scoring scale for muscle strength, grip strength, Inflammatory Rasch-built Overall Disability Scale (I-RODS), 6MWT – Six-minute Walking Test (6MWT), Inflammatory Neuropathy Cause and Treatment (INCAT), Leads Assessment of Neuropathic Symptoms and Signs (LANSS) and Composite Autonomic Symptom Scale 31 (COMPASS31) for autonomic dysfunction detection.

Prevalence and incidence were calculated using population data from the corresponding period of the Central Statistics Bureau of Latvia website [6].

All patients underwent telephone interviews regarding their vaccination status against SARS-CoV-2 infection or history of SARS-CoV-2 infection. The clinical impact of SARS-CoV-2 on the clinical course of the disease was evaluated during a routine follow-up visit.

Patients with other chronic autoimmune neuropathies were not included because of their rarity.

3. RESULTS

3.1. Chronic Inflammatory Demyelinating Polyneuropathy

The prevalence and incidence of CIDP in Latvian populations were 1.21 per 100 000 people and 1.16 per 100 000 people, respectively. The gender distribution was similar - 12 females and 11 males. The median age of CIDP patients at enrollment in this study was 61 years (IQR 53-74). The average age of the patient at the onset of first symptoms was 56 years (range 13-82 years), with the average duration until diagnosis being 13 months.

74% (n=17) of patients initially presented with sensory symptoms, while the remaining part of the group was motor deficits. The course of the disease was more often relapsing-remitting - in 70% of patients (n=16) but monophasic - in 30% of patients (n=7). Only one patient experienced acute onset CIDP. More than half of the patients (61%, n=14) were diagnosed with typical CIDP, while 39% (n=9) were diagnosed with CIDP variants: 23% (n=5) with sensory-predominant CIDP, 13% (n=3) with distal CIDP and 4% (n=1) with multifocal CIDP. The median I-RODS score for the study group was 36 (summed raw score, range 9-48 points). Patient characteristics are shown in Table **1**.

Nerve conduction studies were performed in all patients, of which 91% (n=21/23) fulfilled the current neurophysiological criteria for demyelination in typical CIDP [4]. Lumbar puncture and CSF analysis were done in 13 patients (56%), where 10 patients had elevated CSF protein > 0.5 g/L.

In most patients, 87% (n=20) fulfilled the criteria for CIDP, while 13% (n=3) were diagnosed with possible CIDP.

As the first line therapy, 8 patients received intravenous immunoglobulins (IVIG), 8 patients - plasmapheresis (PEX), 5 patients - subcutaneously administered immunoglobulins (SCIg), and the minority (2 patients) received glucocorticoids (GCs). Currently, 21 CIDP patients are undergoing treatment with SCIg, 2 patients are receiving IVIG, and another two have stable remission and therefore do not receive treatment.

3.2. Multifocal Motor Neuropathy

The point prevalence and incidence of MMN in the Latvian population were 0.42 per 100 000 people and 0.40 per 100 000 people, respectively. In this study, 4 male and 4 female patients were included. The median age of the patients at the time of the study was 46 (IQR 22.75 - 55.75). The average age at the onset of first symptoms was 40 years (range 12-70), with the average time until diagnosis of MMN being 26 months.

Table 1. General characteristics of CIDP patients.

Case	Sex	Age at Onset (years)	First Symptoms	Variant of CIDP	CSF Protein, g/l	Course of Disease	RODS, CIDP, Points RAW	First Line Treatment	Current Treatment
P1	F	76	Sensory	Typical	N/A	Monophasic	36	PLEX	SCIg
P2	M	50	Sensory	Typical	0.36	Relapsing-remitting	47	IVIG	SCIg
P3	M	50	Motor	Typical	N/A	Relapsing-remitting	36	PLEX	SCIg
P4	F	42	Sensory	Predominantly sensory	N/A	Monophasic	46	PLEX	SCIg
P5	F	60	Motor	Typical	0.52	Relapsing-remitting	43	PLEX	None/remission
P6	F	16	Motor	Typical	0.25	Monophasic	39	IVIG	SCIg
P7	M	55	Motor	Predominantly motor	0.56	Relapsing-remitting	30	PLEX	SCIg
P8	M	69	Sensory	Typical	N/A	Relapsing-remitting	48	IVIG	None/remission
P9	M	43	Sensory	Typical: motor > sensory and severe ataxia, bulbar signs	1.57	Relapsing-remitting	9	IVIG	IVIG
P10	F	57	Sensory	Typical	0.4	Relapsing-remitting	28	IVIG	SCIg
P11	M	76	Motor	Typical	1.03	Relapsing-remitting	18	PLEX	SCIg
P12	M	13	Sensory	Typical	0.82	Relapsing-remitting	38	IVIG	IVIG
P13	M	52	Motor	Typical	1.8	Relapsing-remitting	31	PLEX	SCIg
P14	M	68	Sensory	Typical	0.575	Relapsing-remitting	33	IVIG	SCIg
P15	M	52	Sensory	Typical	0.568	Monophasic	42	GCs	SCIg
P16	F	51	Sensory	typical	0.43	Relapsing-remitting	24	PLEX	SCIg
P17	F	56	Sensory	Predominantly sensory	N/A	Relapsing-remitting	42	SCIg	SCIg
P18	F	70	Sensory	Typical	0.62	Relapsing-remitting	36	GCs	SCIg
P19	M	60	Sensory	Distal	1.2	Relapsing-remitting	38	IVIG	SCIg
P20	F	82	Sensory	Distal	N/A	Monophasic	32	SCIg	SCIg
P21	F	60	Sensory	Predominantly sensory	N/A	Monophasic	48	SCIg	SCIg
P22	F	78	Sensory	Predominantly sensory	0.54	Relapsing-remitting	46	SCIg	SCIg
P23	F	52	Sensory	Distal	N/A	Monophasic	36	SCIg	SCIg

Abbreviations: F - female, IVIG - intravenous immunoglobulins, GCs - glucocorticoids, M - male, n/a - not applicable, PLEX - plasmapheresis, SCIg – subcutaneously administered immunoglobulins.

Table 2. General characteristics of MMN patients.

Case	Sex	Age at Onset	First Symptoms	Course of Disease	RODS, MMN, Points RAW	First Line Treatment	Current Treatment
P24	F	42	LA, LL	Monophasic	19	IVIG	SCIg
P25	F	55	LA	Monophasic	34	IVIG	SCIg
P26	M	43	RA	Monophasic	44	IVIG	SCIg
P27	F	12	RA, LA	Relapsing-remitting	43	IVIG	SCIg
P28	M	37	RA	Monophasic	3	IVIG	SCIg
P29	F	70	RA	Relapsing-remitting	22	IVIG	SCIg
P30	M	23	LA	Monophasic	48	SCIg	SCIg
P31	M	34	LA	Monophasic	44	SCIg	SCIg

Abbreviations: F - female, IVIG - intravenous immunoglobulins, M - male, SCIg – subcutaneously administered immunoglobulins.

The first presenting symptom for all patients included the development of motor weakness in the upper extremities. Only one patient initially presented with symptoms involving the lower extremity, particularly the lower leg. Patient characteristics are shown in Table **2**.

In this study, the disease course for 75% of patients (n=6) was monophasic, while 2 patients had relapsing-remitting. Our patient group's median MMN-RODS was 43 (summed raw score, range 3-48).

Nerve conduction studies were performed in all patients, sequentially fulfilling the neurophysiological criteria for MMN. In most cases, the electrophysiological evaluation revealed initial conduction blocks in the median, ulnar, and tibial nerves. Lumbar puncture was performed in 2 patients. CSF protein was 0.29 g/l and 0.523 g/l, respectively.

In most MMN patients, 75% (n=6) received IVIG as first-line therapy. A minority of patients, 25% (n=2), initially already received SCIg. Currently, all MMN patients receive SCIg.

3.3. Impact of SARS-CoV-2

Most patients involved in this study (90%, n=28) with CIDP or MMN have been vaccinated against SARS-CoV-2 infection. 75% (n=21) of patients received mRNA vaccines - Pfizer/BioNTech Comirnaty (n=14) and Spikevax (n=7), and 25% (n=7) - virus vector vaccines Vaxzevria (n=5) and Janssen/Ad26.COV 2.S vaccine (n=2).

In the vaccinated group, only two patients contracted the SARS-CoV-2 infection after immunization and presented with mild symptoms without pneumonia. One of the patients was vaccinated with Pfizer/BioNTech Comirnaty, and the other with Vaxzevria. None of them were hospitalized. One vaccinated patient (who had received the virus vector vaccine, Vaxzevria) experienced a massive functional decrease in muscle strength from 5 to 3 (according to the MRC scale) in both proximal and distal muscle groups just one week after the vaccination when he contracted the SARS-CoV-2 infection.

All non-vaccinated patients (n=3) contracted the SARS-CoV-2 infection and presented with moderate symptoms and pneumonia. Nevertheless, none of these patients experienced any fluctuations or relapse regarding autoimmune polyneuropathy.

4. DISCUSSION

The prevalence and incidence of CIDP in Latvian populations was 1.21 per 100 000 individuals and 1.16 per 100 000 individuals, respectively, since 2015. These findings correspond with data reported by other European countries: CIDP prevalence rate of 2.84 per 100 000 people in England and 3.58 per 100 000 in Italy [7 - 9]. The prevalence of CIDP has been reported as high as 7.7 per 100 000 in Norway and 8.9 per 100 000 individuals in the US [10]. The point prevalence in Latvia was closest to that reported in Japan – 1.61 per 100 000 individuals [11]. It must be noted that the results of these studies were published before the updated CIDP diagnostic criteria and, therefore, may differ. Corresponding with the updated 2021 EFNS/PNS diagnostic criteria for CIDP, the incidence of CIDP in Iceland was reported to be 0.3 per 100,000 person-years of study; however, patients with possible CIDP were excluded from the study [12].

The gender distribution of CIDP patients in Latvia is similar (48% males), contrary to a significant male predominance reported in the other studies [7, 8, 11 - 13]. This could be explained due to the small patient group.

The point prevalence and incidence of MMN in the Latvian population were 0.42 per 100 000 individuals and 0.40 per 100 000 individuals, respectively. Similarly, as with CIDP, this is consistent with data reported by other European countries: MMN prevalence rate of 0.53 per 100 000 people in southeast England, 0.6 in the Netherlands per 100 000 people and 0.7 per 100 000 people in Ireland [8, 10, 14]. In Japan, the reported prevalence rate of MMN was also similar – 0.29 per 100 000 [15].

Gender distribution of MMN patients in reported studies shows male predominance, while in Latvia, half of the patients were male [16]. Three-quarters of MMN patients experienced their first symptoms before 50 years of age, in correspondence with previous studies [16, 17].

While there is currently no comprehensive analysis and explanation for reported epidemiological differences in various geographical regions, a multifactorial influence, including ethnicity, diet, as well as genetic predisposition and diagnostic pathways, likely plays a significant role [10, 18].

There is limited data on SARS-CoV-2 vaccine safety and efficacy in patients with autoimmune neuropathies, particularly in those undergoing immunosuppressive treatment [1]. In our study, vaccination did not negatively impact the course of the disease or lead to exacerbations of symptoms. On the contrary, contracting the SARS-CoV2 infection in a vaccinated individual significantly decreased motor function.

Overall, in our study group, vaccination against SARS-CoV-2 was safe and did not negatively affect the clinical course of chronic autoimmune neuropathy. This is also supported by a review study by Taga *et al.* in 2022, which analyzed the effect of SARS CoV-2 on the new onset and existing autoimmune neuropathies. No data suggests worsening symptoms after SARS-CoV-2 vaccination [19]. While novel cases of neuropathies post-SARS CoV-2 vaccination have been reported, none of the study group patients experienced complications following the vaccination.

Our study has several limitations. The study group included a small number of CIDP and MMN patients, which derives from Latvia's current small population. The small total Latvian population also could explain some of the differences we found in our study group compared to other studies, such as the similar male-to-female ratio in CIDP. These factors will be addressed in future studies. Patients with possible CIDP were also included in the study. It could be possible that more patients contracted the SARS-CoV-2 infection but were asymptomatic or paucisymptomatic; therefore, they did not report the infection.

CONCLUSION

This is the first population-based study of CIDP and MMN in the Baltics, covering the epidemiology of autoimmune neuropathy patients diagnosed from 2015 to 2021 in Latvia.

We report that the prevalence and incidence of CIDP in Latvia was 1.21 per 100 000 individuals and 1.16 per 100 000 individuals. The point prevalence of MMN in Latvia was 0.42 per 100 000 individuals and 0.40 per 100 000 individuals, respectively. These findings correspond to other epidemiological reports regarding CIDP and MMN in Europe.

Vaccination against SARS-CoV-2 in our study group was safe and did not negatively impact the clinical course of chronic autoimmune neuropathy. No adverse events following vaccination were observed in our patients.

LIST OF ABBREVIATIONS

GMWT	=	6MWT
CIDP	=	Chronic Inflammatory Demyelinating Polyneuropathy
COMPASS 31	=	Composite Autonomic Symptom Scale 31
GCs	=	Glucocorticoids
I-RODS	=	Inflammatory Rasch-built Overall Disability Scale
INCAT	=	Inflammatory Neuropathy Cause and Treatment
IVIG	=	Intravenous Immunoglobulin

LANSS	=	Leeds Assessment of Neuropathic Symptoms and Signs
MMN	=	Multifocal Motor Neuropathy
MRC	=	Medical Research Council
PLEX	=	Plasmapheresis
SCIg	=	Subcutaneously Administered Immunoglobulins

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Central Medical Ethics Committee of Latvia approval Nr.3/18-03-21.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were per the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2008.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the corresponding author, [M.L.k] on special request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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