SHORT COMMUNICATION

Cranial nerve involvement in typical and atypical chronic inflammatory demyelinating polyneuropathies

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Background and purpose: Cranial nerve palsy is occasionally present in patients with chronic inflammatory demyelinating polyneuropathy (CIDP), but its prevalence, characteristics and relations with the CIDP subtypes have rarely been investigated. The aim of this study was to systematically assess cranial nerve involvement in typical and atypical CIDP.

Methods: Clinical data were reviewed in 132 consecutive patients with CIDP, including typical CIDP (n = 89), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) (n = 31), distal acquired demyelinating symmetric (DADS) (n = 9) and others (n = 3).

Results: The frequency of cranial nerve palsy was 11% in typical CIDP, 48% in MADSAM and 11% in DADS. Facial and bulbar palsy was most frequently present (9%), followed by ocular motor nerve palsy (5%). Bilateral involvement was seen in all typical CIDP and DADS patients, whereas 80% of MADSAM patients had unilateral palsy. The presence of cranial nerve involvement was associated with more severe limb muscle weakness in typical CIDP, but not in MADSAM. Cranial nerve palsy fully recovered in 90% of typical CIDP and in 67% of MADSAM patients.

Conclusion: Amongst the CIDP subtypes, cranial palsy is frequent and unilateral in MADSAM, and less frequent and bilateral in typical CIDP and DADS. In typical CIDP, facial and bulbar palsy reflects more severe and extensive inflammation.

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare immune-mediated neuropathy, characterized by a relapsing–remitting course and evidence of peripheral nerve demyelination [1]. Recent advances in immunological, neurophysiological and neuroimaging research have disclosed several different pathomechanisms according to the subtypes of CIDP [1–6]. The European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria proposed clinical subtypes, such as typical CIDP, multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), distal acquired demyelinating symmetric (DADS) and others, based on clinical manifestations [7]. Different therapeutic responses amongst these clinical subtypes support the hypothesis that different pathogeneses potentially underlie each subtype [8–10].

Cranial nerve (CN) palsy in CIDP has been described in several case series or reports, but its prevalence, characteristics, prognosis and relations with the CIDP subtypes have rarely been systematically reported. A prior study in 60 CIDP patients disclosed that 13% of patients had facial weakness and 3% had extraocular muscle impairment [11]. Another study examined clinical and electrophysiological profiles in 92 CIDP patients and showed CN palsy in 16% patients, who had facial weakness in 15% of patients, bulbar palsy in 6% and ophthalmoplegia in

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4% [12]. However, the relations with the CIDP subtypes have rarely been described. Patterns and severity of CN involvement could be different in each CIDP subtype, reflecting the different pathogenesis.

The present study focused on CN palsy in CIDP and aimed to disclose its prevalence, characteristics, prognosis and relations with the CIDP subtypes.

Methods

Subjects and their evaluations

A total of 132 patients, who were seen at the Chiba University Hospital between 1984 and 2019, were included in this study. They fulfilled EFNS/PNS criteria for probable or definite CIDP and were followed up for at least 1 year [13]. Patients with anti-myelin-associated glycoprotein or sulfated glucuronyl paragloboside antibodies and multifocal motor neuropathy were excluded. The CIDP patients were classified into the clinical subtypes typical, MADSAM, DADS and others, according to EFNS/PNS criteria [13]. In the present study, MADSAM was defined as typical mononeuropathy multiplex or asymmetric weakness with one or more Medical Research Council scale differences in the homonymous muscles [14].

Functional disability was assessed using the Hughes functional grading scale: 0, normal; 1, able to run; 2, able to walk 5 m independently; 3, able to walk 5 m with aids; 4, chair or bed bound [15]. The presence of CN palsy was clinically evaluated, and CN palsy which developed in the progressive phase was judged as CIDP-related CN palsy. XI nerve palsy was excluded from the present study because trapezius or sternocleidomastoid muscles are predominantly innervated by the upper cervical spinal nerves.

Statistical analysis

All statistical analyses were performed by one of the authors (KS) using SPSS Version 24 software (Chicago, IL, USA). Differences between the typical CIDP and MADSAM cohorts were analyzed, using the unpaired *t* test or Fisher's exact test. Additionally, typical CIDP and MADSAM patients were divided into two groups according to the presence of cranial neuropathy. In these analyses, the DADS cohort was excluded due to the small number of patients. Differences in these groups were also analyzed, using an unpaired *t* test or Fisher's exact test. Data are presented as mean ± SD. The level of statistical significance was established at $P < 0.05$.

Results

Clinical profiles of 132 CIDP patients are described in Table 1. Of these, 89 patients were classified as having typical CIDP, 31 as MADSAM, nine as DADS, and the remaining three were classified as others (pure sensory or focal). Disease duration in the MADSAM group was longer than the typical CIDP group ($P = 0.037$), whereas functional disabilities in typical CIDP at first visit were more severe than MADSAM patients ($P = 0.049$). CN palsy was found in 48% of the MADSAM patients and only in 11% of typical CIDP ($P = 0.000002$). Additionally, it was also rare in DADS (11%) and others (0%).

Involved CNs are shown in Table 2. Facial and bulbar palsy (IX and X) were the most frequent symptom in CIDP (9%), followed by oculomotor palsy (III and VI; 5%), but the others were rare: loss of facial sensation (V) (3%), hearing loss (VIII) (2%) and optic neuritis (II) (1%). Whilst all of the CN palsy patients in typical CIDP and DADS were bilateral, 80% of MADSAM patients had unilateral palsy. CN palsy in typical CIDP was fully recovered in 90% of patients, whereas that in MADSAM was not recovered in 33% of patients. Therapies for patients with CN palsy, such as corticosteroids, immunoglobulin and plasmapheresis, were similarly performed in typical CIDP and MADSAM patients. CN palsy in one DADS patient was fully recovered.

The characteristics of CIDP with and without CN palsy in typical CIDP and MADSAM were analyzed. Gender, age at first visit, disease duration and functional disabilities at first visit in patients with and without CN palsy were similar in both subtypes. Functional disabilities at last visit in typical CIDP with CN palsy (1.8 ± 0.7) were more severe than in patients without CN palsy (1.1 ± 0.7) ($P = 0.019$). Similar trends were found in MADSAM (CN+ 1.9 ± 2.0, CN– 0.9 ± 0.9), but they did not reach significant differences ($P = 0.11$).

Discussion

Our results show that the frequency of CN involvement is largely dependent on the CIDP subtype: less frequent in typical CIDP and DADS, and frequent in MADSAM. In all subtypes, the facial and bulbar nerves are often affected, but the involvement was bilateral in typical CIDP and DADS and unilateral in MADSAM. Moreover, CN palsies in typical CIDP and DADS recovered well, but they were often refractory in MADSAM. The different patterns and

Table 1 Clinical characteristics of 132 CIDP patients according to clinical subtypes

	Typical CIDP (n = 89)	MADSAM (n = 31)	DADS (n = 9)	Others (n = 3)	P value (typical versus MADSAM)
Male:female	54:35	18:13	9:0	2:1	0.83
Age at first visit (years)	48.0 (18.7)	43.4 (19.7)	61.2 (15.9)	75.3 (8.5)	0.27
Disease duration (months)	21.0 (45.2)	51.2 (71.9)	36.8 (65.6)	61.0 (75.0)	0.037
Hughes functional scale at first visit	2.1 (1.0)	1.6 (1.2)	2.8 (0.8)	2.7 (0.9)	0.049
Hughes functional scale at last visit	1.1 (0.8)	1.4 (1.6)	1.8 (0.9)	2.7 (1.2)	0.40
Cranial nerve palsy (%)	11%	48%	11%	0%	0.000002

CIDP, chronic inflammatory demyelinating polyneuropathy; DADS, distal acquired demyelinating symmetric; MADSAM, multifocal acquired demyelinating sensory and motor. Data are given as mean (SD).

Table 2 Involved cranial nerve palsy in CIDP

Cranial nerve involved	Typical (n = 89)	MADSAM (n = 31)	DADS (n = 9)
I	0	0	0
II	0	1	0
III	1[a]	3	0
IV	0	0	0
V	2[a]	2	0
VI	0	3	0
VII	7[a]	4 (1 bilateral)	0
VIII	0	2 (1 bilateral)	0
IX, X	6[a]	5 (4 bilateral)	1[a]
XII	0	0	0

CIDP, chronic inflammatory demyelinating polyneuropathy; DADS, distal acquired demyelinating symmetric; MADSAM, multifocal acquired demyelinating sensory and motor. [a]All bilateral.

prognosis of CN palsy reflect the different pathogenesis in each subtype of CIDP.

Previous studies have shown that CN palsy is present in approximately 10%–20% of CIDP patients, but the CIDP subtypes were rarely taken into account [12,16,17]. In the present study, the prevalence (11%) was similar in typical CIDP, but substantially higher (48%) in MADSAM. Classical CIDP, which was advocated in the 1970s, is characterized with symmetric weakness, involving proximal as well as distal limbs, currently termed typical CIDP [16], and in 2005 the EFNS/PNS guideline proposed inclusion of atypical CIDP [13]. Therefore, prior studies published before 2005 in particular, which reported a low prevalence of CN palsy, might not include atypical forms.

Cranial nerve palsy in typical CIDP was bilateral and well recovered but was unilateral and relatively refractory in MADSAM; these findings are similar to those of the limb muscles. As mentioned above, typical CIDP is characterized by symmetric limb weakness. Additionally, patients with typical CIDP respond well to immunomodulatory treatments [15], but up to 30% of MADSAM patients are refractory to any immunomodulatory treatments and experience chronic progressive course presumably because of development of axonal damage during the long course of the disorder [15]. As such, the differences in the characteristics and prognosis of CN palsy amongst CIDP clinical subtypes may be similar to those of limb muscles.

Facial and bulbar palsy were most common, irrespective of the CIDP subtype: typical CIDP and MADSAM. This trend is similar to those of previous studies [12,16]. The reason why these nerves are preferentially affected remains unknown. However, several studies reported subclinical involvement of CNs in CIDP. A previous study investigated trigeminal and facial nerve involvement in CIDP, using neurophysiological techniques, and showed abnormal blink reflex in 85% of patients [18]. Additionally, subclinical hypertrophy in CNs has frequently been reported [19]. Most CIDP patients may have CN involvement, and some of them may express symptoms. The finding that the presence of CN palsy is associated with more functional disabilities in typical CIDP, shown in this study, may support this speculation. However, the reason for less severe involvement of CN than spinal nerves is also unknown, but potentially the target epitope expression may be different.

In the present study electrophysiological evaluation was not systematically performed in cranial regions and could not detect subclinical CN involvement. This is a limitation of this retrospective study.

In CIDP, it is important to recognize the pattern of CN involvement in clinical practice and in understanding the underlying pathogenesis of CIDP.

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Disclosure of conflicts of interest

None declared.

Ethical approval

Informed consent has been given by the subjects. This study was approved by the Ethics Committee of Chiba University School of Medicine.

Originality of submitted research

The content is not published or under review with any other publication.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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