Table 5. Comparison of age at onset with CSF findings and OCBs in MS patients from Hokkaido and Kyushu.

Region	CSF findings[a]		*p* value
	Positive	Negative	
Hokkaido ($n = 180$)	29.9 ± 10.1 ($n = 133$)	30.7 ± 11.8 ($n = 47$)	n.s.
Kyushu ($n = 184$)	31.6 ± 12.7 ($n = 80$)	32.0 ± 13.3 ($n = 104$)	n.s.
Region	OCB		*p* value
	Positive	Negative	
Hokkaido ($n = 147$)	29.9 ± 9.3 ($n = 93$)	31.7 ± 12.1 ($n = 54$)	n.s.
Kyushu ($n = 181$)	32.2 ± 12.7 ($n = 75$)	31.2 ± 13.2 ($n = 106$)	n.s.

Values of age at onset are presented as mean ± SD. [a] Positive CSF findings: oligoclonal IgG band (OCB) positivity and/or elevated IgG index; negative CSF findings: neither presence of OCBs nor elevated IgG index. CSF: cerebrospinal fluid; MS: multiple sclerosis; Ig: immunoglobulin; n.s.: not significant.

Table 6. Comparison of MSSS with CSF findings and OCBs in MS patients from Hokkaido and Kyushu.

Region	CSF findings[a]		*p* value
	Positive	Negative	
Hokkaido ($n = 178$)	3.4 ± 2.9 ($n = 132$)	2.6 ± 2.8 ($n = 46$)	n.s.
Kyushu ($n = 182$)	4.9 ± 2.8 ($n = 79$)	4.4 ± 3.1 ($n = 103$)	n.s.
Region	OCB		*p* value
	Positive	Negative	
Hokkaido ($n = 145$)	3.4 ± 3.0 ($n = 93$)	3.2 ± 3.0 ($n = 52$)	n.s.
Kyushu ($n = 179$)	5.0 ± 2.7 ($n = 74$)	4.4 ± 3.1 ($n = 105$)	n.s.

Values of MSSS are presented as mean ± SD. [a]Positive CSF findings: oligoclonal IgG band (OCB) positivity and/or elevated IgG index; negative CSF findings: neither presence of OCBs nor elevated IgG index. CSF: cerebrospinal fluid; MS: multiple sclerosis; Ig: immunoglobulin; n.s.: not significant; MSSS: Multiple Sclerosis Severity Score.

been observed in Western countries.[7] Thus, the latitude of the region in which MS patients reside may be a factor inducing OCB production. On the other hand, OCB positivity, even in Hokkaido, was not as high as that recorded in Western countries, where it is has been reported to be >90%.[7] The four dichotomized magnetic resonance imaging (MRI) parameters proposed by Barkhof et al.:[25] (1) the presence of at least one gadolinium-enhancing lesion or nine T2 hyperintense lesions, (2) the presence of at least one infratentorial lesion, (3) the presence of at least one juxtacortical lesion, and (4) the presence of at least three periventricular lesions, are highly accurate for the diagnosis of MS in patients with a clinically isolated syndrome in Western countries.[29] OCB positivity was slightly higher in patients with Barkhof brain lesions; however, OCB positivity, even in typical MS patients, did not reach the rate observed in Western countries.

The *HLA-DRB1*04:05* allele is reportedly a risk factor for younger age at disease onset, lower EDSS scores, and lower frequencies of MS-like brain lesions among Japanese MS patients.[15] Furthermore, it has been reported that *HLA-DRB1*04:05*-positive MS patients have a tendency for lower frequencies of OCB positivity/increased IgG index compared with *HLA-DRB1*04:05*-negative MS patients,[15] and *HLA-DRB1*04:05* has been associated with OCB-negative MS in Japanese populations.[8] Similar findings have been reported in Sweden, where the *HLA-DRB1*04:04* allele has been associated with OCB-negative MS patients, although the *HLA-DRB1*04:05* allele is rare in northern Europe.[16] *HLA-DRB1*04:04* and **04:05* alleles are closely related in terms of genetic sequence.[30] It has been speculated that the two genomic-level associations share the same functional basis and that OCB-negative MS is the same entity across populations.[16] On the other hand, there is a strong association between the *HLA-DRB1*15* allele and OCB positivity,[13,17,18] and an association between the *DRB1*1501* allele and higher levels of CSF inflammation, as assessed by IgG synthesis levels.[31] In the present study, *HLA-DRB1*15:01*-positive MS patients without the *HLA-DRB1*04:05* allele exhibited a

significantly higher prevalence of OCB positivity than *HLA-DRB1*04:05*-positive MS patients without the *HLA-DRB1*15:01* allele. In addition, logistic regression analysis revealed that MS patients who carried the *HLA-DRB1*15:01* allele exhibited a trend for being at a higher risk of OCB positivity, whereas those who carried the *HLA-DRB1*04:05* allele were at a lower risk. In other words, it was considered that the *HLA-DRB1*15:01* allele has a positive impact on the frequency of OCB positivity/increased IgG index and that *HLA-DRB1*04:04* and **04:05* alleles have a negative impact on the frequency of OCB positivity. However, there is no clear latitudinal distribution of the *HLA-DRB1*15:01* allele globally,[13] and our data demonstrated that the phenotype frequencies of *HLA-DRB1*04:05* and **15:01* alleles are similar between Hokkaido and Kyushu. Taken together, our results suggest that latitude and *HLA-DRB1* alleles have an independent impact on the emergence of CSF IgG abnormalities in Japanese patients with MS.

Regarding the difference in positive CSF findings or OCB positivity between patients from Hokkaido and Kyushu, factors other than *HLA-DRB1*04:05* and **15:01* alleles may influence the latitudinal differences observed for these CSF findings. An alternative hypothesis is that sunlight exposure and/or vitamin D status influence the propensity to develop central nervous system (CNS)-resident oligoclonal B-cell populations that are responsible for OCB synthesis.[13] In addition, a distinct infection rate of ubiquitous pathogens, such as *Helicobacter pylori* and *Chlamydia pneumoniae*, between Hokkaido and Kyushu may underlie the latitudinal differences in CNS IgG abnormalities in MS patients, because these bacteria can affect this parameter.[32]

It has been reported that OCBs are associated with a worse MS prognosis.[13,33,34] However, no significant difference in prognosis between OCB-positive and -negative MS patients has been reported.[16,35] A Japanese study reported no significant differences in disease prognosis (which was evaluated using the progression index) between OCB-positive and -negative MS patients.[8] In the current study, disease prognosis evaluated using MSSS was not significantly different between OCB-positive and -negative MS patients both in Hokkaido and Kyushu. Thus, in Japanese MS patients, disease progression may not be affected by the presence of OCBs.

Regarding the association between age at onset and OCB positivity, a previous study reported that MS patients with OCBs have younger age at onset than OCB-negative patients.[13] However, another study found no significant differences in age at onset, although there was a trend in favor of younger age at onset in OCB-positive patients ($p = 0.0866$).[35] In our study, no significant differences in age at disease onset were found in patients from Hokkaido or Kyushu. These contrasting results between the studies may be due to the differences in sample size or ethnic background. Further studies are required to address the association between age at onset and OCB positivity.

It is considered that OCBs are not merely the terminal result of a targeted immune response in MS; rather, they represent a component of active B-cell immunity that is dynamically supported on both sides of the blood-brain barrier[36] and result from intrathecal antigen-driven immune responses.[37] However, the target antigens remain unclear and the pathological significance of intrathecally produced IgG remains speculative.[12] The reasons for the existence of latitudinal and regional/ethnic differences in OCB positivity remain unclear, and it is speculated that some environmental factors (e.g. vitamin D) may be responsible. Further studies are required to address the immunological function of OCBs.

In this study, sample collection was not entirely randomized, and the sample size was only moderate. These factors are potential limitations to this study and might not provide data representative of the entire country. Data in several other regions between Hokkaido and Kyushu are needed to confirm differences of OCB positivity by latitude in Japan. On the other hand, the sensitivity of IgG index is lower than that by detection of CSF OCB in MS;[26] however, in our study, the sensitivity of "positive CSF findings" was higher than that of OCB positivity. The exact reason is unclear; however, ethnic differences may have affected the result. Further studies are required to answer these questions.

In conclusion, our study indicates that a north-south gradient in OCB positivity in MS patients may be common in Japan and Western countries, although OCB positivity in Japan, even in northern Japan, where a high prevalence of OCB positivity was shown, is lower than that observed in Western countries. The *HLA-DRB1*15:01* allele is facilitative, whereas the *HLA-DRB1*04:05* allele is protective for abnormal IgG production in Japanese MS patients regardless of the latitude.

Acknowledgement
We thank Eri Takahashi for her skillful technical assistance.

Conflicts of interest

Dr Niino has received funding for travel and/or speaker honoraria from Biogen Idec, Bayer Schering Pharma, Mitsubishi Tanabe Pharma Corporation, and Novartis Pharma; is part of a scientific advisory board for Biogen Idec; and has received research support from Grants-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare of Japan.

Dr Fukazawa serves/has served on scientific advisory boards for Bayer Pharma, Biogen Idec, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Company, and Novartis Pharma; and has received funding for travel and speaker honoraria from Bayer Pharma, Biogen Idec, Mitsubishi Tanabe Pharma Corporation, and Novartis Pharma.

Dr Houzen serves on scientific advisory boards for Biogen Idec, Novartis Pharma, and Mitsubishi Tanabe Pharma Corporation.

Dr Miyazaki has received speaker honoraria and research material from Novartis Pharma as well as research support from the Japan Multiple Sclerosis Society.

Dr Shimohama has received speaker honoraria from Novartis Pharma, Boehringer Ingelheim, Kyowa Hakko Kirin, Dainippon Sumitomo Pharma, Takeda Pharmaceutical Company, Daiichisankyo Pharma, Jansen Pharma, Eisai Pharma, Biogen Idec, and Mitsubishi Tanabe Pharma Corporation; and he has received research support from Grants-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare of Japan and the Smoking Research Foundation.

Dr Kikuchi has received speaker honoraria from Novartis Pharma, Boehringer Ingelheim, Kyowa Hakko Kirin, Dainippon Sumitomo Pharma, and FP Pharmaceutical Corporation; he serves on the scientific advisory board for Novartis Pharma; and he has received research support from Grants-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare of Japan and the National Hospital Organization of Japan.

Dr Kira is a consultant for Biogen Idec Japan, has received honoraria from Bayer Healthcare and funding for a trip from Bayer Healthcare and Biogen Idec Japan, and is funded by a Research Grant for Nervous and Mental Disorders from the Ministry of Health, Labor and Welfare, Japan, as well as grants from the Japan Science and Technology Agency and the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Drs Sato, Yoshimura, Hisahara, Matsushita, Isobe, and Yoshida have nothing to declare.

Funding

This work was supported in part by a Health and Labor Sciences Research Grant on Intractable Diseases (Neuroimmunological Diseases) from the Ministry of Health, Labor and Welfare of Japan, and a grant-in-aid (B; no. 22390178) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

1. Melcon MO, Correale J and Melcon CM. Is it time for a new global classification of multiple sclerosis? *J Neurol Sci* 2014; 344: 171–181.
2. Houzen H, Niino M, Hirotani M, et al. Increased prevalence, incidence, and female predominance of multiple sclerosis in northern Japan. *J Neurol Sci* 2012; 323: 117–122.
3. Osoegawa M, Kira J, Fukazawa T, et al. Temporal changes and geographical differences in multiple sclerosis phenotypes in Japanese: Nationwide survey results over 30 years. *Mult Scler* 2009; 15: 159–173.
4. Kira J. Multiple sclerosis in the Japanese population. *Lancet Neurol* 2003; 2: 117–127.
5. Stangel M, Fredrikson S, Meinl E, et al. The utility of cerebrospinal fluid analysis in patients with multiple sclerosis. *Nat Rev Neurol* 2013; 9: 267–276.
6. Cavuoti D, Baskin L and Jialal I. Detection of oligoclonal bands in cerebrospinal fluid by immunofixation electrophoresis. *Am J Clin Pathol* 1998; 109: 585–588.
7. Dobson R, Ramagopalan S, Davis A, et al. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: A meta-analysis of prevalence, prognosis and effect of latitude. *J Neurol Neurosurg Psychiatry* 2013; 84: 909–914.
8. Kikuchi S, Fukazawa T, Niino M, et al. HLA-related subpopulations of MS in Japanese with and without oligoclonal IgG bands. *Neurology* 2003; 60: 647–651.
9. Nakashima I, Fujihara K, Sato S, et al. Oligoclonal IgG bands in Japanese patients with multiple sclerosis. A comparative study between isoelectric focusing with IgG immunofixation and high-resolution agarose gel electrophoresis. *J Neuroimmunol* 2005; 159: 133–136.
10. Chang KH, Lyu RK, Chen CM, et al. Clinical characteristics of multiple sclerosis in Taiwan: A cross-sectional study. *Mult Scler* 2006; 12: 501–506.
11. Li B, Dong H, Zhang J, et al. Cerebrospinal fluid IgG profiles and oligoclonal bands in Chinese patients with multiple sclerosis. *Acta Neurol Scand* 2007; 115: 319–324.

12. Petzold A. Intrathecal oligoclonal IgG synthesis in multiple sclerosis. *J Neuroimmunol* 2013; 262: 1–10.

13. Lechner-Scott J, Spencer B, de Malmanche T, et al. The frequency of CSF oligoclonal banding in multiple sclerosis increases with latitude. *Mult Scler* 2012; 18: 974–982.

14. Giovannoni G and Ebers G. Multiple sclerosis: The environment and causation. *Curr Opin Neurol* 2007; 20: 261–268.

15. Yoshimura S, Isobe N, Yonekawa T, et al. Genetic and infectious profiles of Japanese multiple sclerosis patients. *PLoS One* 2012; 7: e48592.

16. Imrell K, Landtblom AM, Hillert J, et al. Multiple sclerosis with and without CSF bands: Clinically indistinguishable but immunogenetically distinct. *Neurology* 2006; 67: 1062–1064.

17. Romero-Pinel L, Martínez-Yélamos S, Bau L, et al. Association of *HLA-DRB1*15* allele and CSF oligoclonal bands in a Spanish multiple sclerosis cohort. *Eur J Neurol* 2011; 18: 1258–1262.

18. Wu JS, Qiu W, Castley A, et al. Presence of CSF oligoclonal bands (OCB) is associated with the *HLA-DRB1* genotype in a West Australian multiple sclerosis cohort. *J Neurol Sci* 2010; 288: 63–67.

19. Fukazawa T, Kikuchi S, Sasaki H, et al. The significance of oligoclonal bands in multiple sclerosis in Japan: Relevance of immunogenetic backgrounds. *J Neurol Sci* 1998; 158: 209–214.

20. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.

21. Wingerchuk DM, Lennon VA, Pittock SJ, et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006; 66: 1485–1489.

22. Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. The spectrum of neuromyelitis optica. *Lancet Neurol* 2007; 6: 805–815.

23. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An Expanded Disability Status Scale (EDSS). *Neurology* 1983; 33, 1444–1452.

24. Roxburgh RH, Seaman SR, Masterman T, et al. Multiple Sclerosis Severity Score: Using disability and disease duration to rate disease severity. *Neurology* 2005; 64: 1144–1151.

25. Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997; 120: 2059–2069.

26. Link H and Huang YM. Oligoclonal bands in multiple sclerosis cerebrospinal fluid: An update on methodology and clinical usefulness. *J Neuroimmunol* 2006; 180: 17–28.

27. Kira J, Kanai T, Nishimura Y, et al. Western versus Asian types of multiple sclerosis: Immunogenetically and clinically distinct disorders. *Ann Neurol* 1996; 40: 569–574.

28. Matsushita T, Matsuoka T, Isobe N, et al. Association of the *HLA-DPB1*0501* allele with anti-aquaporin-4 antibody positivity in Japanese patients with idiopathic central nervous system demyelinating disorders. *Tissue Antigens* 2009; 73: 171–176.

29. Tintoré M, Rovira A, Martínez MJ, et al. Isolated demyelinating syndromes: Comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. *AJNR Am J Neuroradiol* 2000; 21: 702–706.

30. Zanelli E, Breedveld FC and de Vries RR. HLA class II association with rheumatoid arthritis: Facts and interpretations. *Hum Immunol* 2000; 61: 1254–1261.

31. Sellebjerg F, Jensen J, Madsen HO, et al. *HLA DRB1*1501* and intrathecal inflammation in multiple sclerosis. *Tissue Antigens* 2000; 55: 312–318.

32. Yoshimura S, Isobe N, Matsushita T, et al. Genetic and infectious profiles influence cerebrospinal fluid IgG abnormality in Japanese multiple sclerosis patients. *PLoS One* 2014; 9: e95367.

33. Avasarala JR, Cross AH and Trotter JL. Oligoclonal band number as a marker for prognosis in multiple sclerosis. *Arch Neurol* 2001; 58: 2044–2045.

34. Joseph FG, Hirst CL, Pickersgill TP, et al. CSF oligoclonal band status informs prognosis in multiple sclerosis: A case control study of 100 patients. *J Neurol Neurosurg Psychiatry* 2009; 80: 292–296.

35. Siritho S and Freedman MS. The prognostic significance of cerebrospinal fluid in multiple sclerosis. *J Neurol Sci* 2009; 279: 21–25.

36. Bankoti J, Apeltsin L, Hauser SL, et al. In multiple sclerosis, oligoclonal bands connect to peripheral B-cell responses. *Ann Neurol* 2014; 75: 266–276.

37. Obermeier B, Lovato L, Mentele R, et al. Related B cell clones that populate the CSF and CNS of patients with multiple sclerosis produce CSF immunoglobulin. *J Neuroimmunol* 2011; 233: 245–248.

JNNP Online First, published on February 11, 2015 as 10.1136/jnnp-2014-309831

RESEARCH PAPER

A nationwide survey of combined central and peripheral demyelination in Japan

Hidenori Ogata,[1] Dai Matsuse,[1] Ryo Yamasaki,[2] Nobutoshi Kawamura,[1,3] Takuya Matsushita,[2] Tomomi Yonekawa,[1] Makoto Hirotani,[4] Hiroyuki Murai,[1] Jun-ichi Kira[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2014-309831).

[1]Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[2]Department of Neurological Therapeutics, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[3]Department of Neurology, Kawamura Hospital, Gifu, Japan
[4]Department of Neurology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Correspondence to
Professor Jun-ichi Kira, Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan; kira@neuro.med.kyushu-u.ac.jp

Received 31 October 2014
Revised 30 December 2014
Accepted 18 January 2015

To cite: Ogata H, Matsuse D, Yamasaki R, *et al*. *J Neurol Neurosurg Psychiatry* Published Online First: [*please include* Day Month Year] doi:10.1136/jnnp-2014-309831

ABSTRACT

Objectives To clarify the clinical features of combined central and peripheral demyelination (CCPD) via a nationwide survey.

Methods The following characteristics were used to define CCPD: T2 high-signal intensity lesions in the brain, optic nerves or spinal cord on MRI, or abnormalities on visual-evoked potentials; conduction delay, conduction block, temporal dispersion or F-wave abnormalities suggesting demyelinating neuropathy based on nerve conduction studies; exclusion of secondary demyelination. We conducted a nationwide survey in 2012, sending questionnaires to 1332 adult and paediatric neurology institutions in Japan.

Results We collated 40 CCPD cases, including 29 women. Age at onset was 31.7±14.1 years (mean±SD). Sensory disturbance (94.9%), motor weakness (92.5%) and gait disturbance (79.5%) were common. Although cerebrospinal fluid protein levels were increased in 82.5%, oligoclonal IgG bands and elevated IgG indices were detected in 7.4% and 18.5% of cases, respectively. Fifteen of 21 patients (71.4%) had abnormal visual-evoked potentials. Antineurofascin 155 antibodies were positive in 5/11 (45.5%). Corticosteroids, intravenous immunoglobulins and plasmapheresis resulted in an 83.3%, 66.7% and 87.5% improvement, respectively, whereas interferon-β was effective in only 10% of cases. CCPD cases with simultaneous onset of central nervous system (CNS) and peripheral nervous system (PNS) involvement exhibited greater disability, but less recurrence and more frequent extensive cerebral and spinal cord MRI lesions compared to those with temporarily separated onset, whereas optic nerve involvement was more common in the latter.

Conclusions CCPD shows different characteristics from classical demyelinating diseases, and distinctive features exist between cases with simultaneous and temporarily separated onset of CNS and PNS involvement.

INTRODUCTION

Inflammatory demyelinating diseases are immune-mediated inflammatory disorders of the nervous system, which are divided into two categories: those affecting the central nervous system (CNS), such as acute disseminated encephalomyelitis and multiple sclerosis (MS) and those affecting the peripheral nervous system (PNS), including Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Demyelinating diseases usually affect either the CNS or PNS, possibly because the relevant autoimmune cells recognise only CNS or PNS antigens. However, it has occasionally been reported that patients with demyelination in the CNS or PNS also exhibit demyelination in the other nervous system. It was reported that 13 of 150 patients with MS had symptoms related to peripheral neuropathy and 4 had demyelinating polyneuropathy.[1] In addition, 5 of 100 patients with CIDP had symptomatic CNS involvement.[2] Demyelinating conditions affecting both the CNS and PNS are described using various diagnostic names, such as combined central and peripheral demyelination (CCPD), CIDP with CNS involvement and CIDP with multifocal CNS demyelination.[3] Although case reports or a small series of studies of such cases have been repeatedly found in the literature,[4–17] whether such conditions represent a distinct disease entity remains to be determined. Since large-scale epidemiological studies on this condition have never before been performed, we conducted a nationwide survey in Japan to uncover the demographic features of CCPD.

METHODS

Procedures

In this survey, CCPD was defined as fulfilling the following criteria:

1. CNS involvement criterion: T2 high-signal intensity lesions in the brain, optic nerves or spinal cord on MRI, or abnormalities on visual-evoked potentials (VEPs).
2. PNS involvement criterion: conduction delay, conduction block, temporal dispersion or F-wave abnormalities, suggesting peripheral demyelinating neuropathy according to nerve conduction studies (NCS). In the present study, it was mandatory that among median, ulnar and tibial nerves, at least two nerves had the aforementioned abnormal findings suggestive of demyelination.
3. Exclusion criterion: secondary demyelinating diseases or changes, such as infectious diseases (eg, human T lymphocyte trophic virus type 1-associated myelopathy, syphilis, neuroborreliosis, HIV infection or progressive multifocal leucoencephalopathy), pre-existing inflammatory diseases (eg, sarcoidosis, Behçet's disease, Sjögren's syndrome, vasculitis or other collagen diseases), mitochondrial disease, metabolic/toxic

diseases (eg, vitamin deficiency, amyloidosis, chronic alcoholism, diabetes mellitus or subacute myelo-opticoneuropathy due to clioquinol intoxication, cervical spondylotic myelopathy, syringomyelia, spinocerebellar degeneration, multiple myeloma, other tumours, inherited diseases (eg, leucodystrophies), cerebrovascular disease and non-specific lesions on T2-weighted MRI (eg, leucoaraiosis). In our previous study on CCPD,[18] all seven CCPD cases fulfilled the EFNS/PNS criteria for CIDP and six cases met the McDonald criteria (2011) for MS.[19 20] Therefore, we did not exclude patients who eventually met either MS or CIDP criteria for the present survey.

Patients with CCPD who visited adult or paediatric neurologists between 2007 and 2011, and met the aforementioned diagnostic criteria were surveyed in 2012. The survey was conducted in two steps. First, a primary questionnaire sheet was sent to 1332 institutions in Japan, which included educational facilities accredited by the Japanese Society of Neurology, neurology departments with two or more board-certified neurologists, neurology departments in hospitals with more than 500 beds, paediatric departments in hospitals with any board-certified paediatric neurologist and departments of paediatrics in medical schools. A response was received from 671 institutions (50.3%), of which 41 institutions reported 57 cases. In the second step, a survey using a detailed questionnaire sheet about each patient was sent to the institutions that reported the CCPD cases. This questionnaire requested the age at onset, sex, history of preceding diseases, habitation area, mode of onset, clinical signs and symptoms, Hughes functional scale scores (grade 0: normal; grade 1: minimal symptoms and signs, able to run; grade 2: able to walk 5 m independently; grade 3: able to walk 5 m with the use of aids; grade 4: chairuser or bedbound; grade 5: requires assisted ventilation; grade 6: dead)[21] at the peak and in remission, laboratory findings, MRI findings of the brain and spinal cord, VEP and NCS findings, differential diagnosis, clinical course, treatment and outcomes. In this second survey, 54 of 57 cases (94.7%) were collated from 38 institutions (92.7%).

Among 54 cases collated, 14 cases were excluded for the following reasons: four cases did not meet CNS involvement criteria; four cases did not meet PNS involvement criteri/a; two cases lacked basic clinical data; two cases were experienced outside the term of this survey; and two cases were strongly suspected of having other diseases (cerebral vascular disease in one and leucodystrophy in another). In the present survey, CNS and PNS symptoms developed less than 2 months apart were regarded as simultaneous or sequential onset of both CNS and PNS involvement. The mode of onset was defined as acute (reaching a maximum intensity within 1 week), subacute (reaching a maximum intensity after 1 week to 1 month) or chronic (reaching a maximum intensity after 1 month).

Statistical analysis

Continuous variables were summarised by descriptive statistics, and categorical variables were summarised using counts of patients and percentages. For comparisons between two groups, qualitative variables were analysed using Fisher's exact test. Continuous variables that followed a parametric distribution were analysed with Student's t tests, whereas non-parametric variables were analysed with the Mann-Whitney U test.

RESULTS

Baseline characteristics

The demographic features of 40 patients with CCPD are summarised in table 1. The mean age at onset was 31.7±14.1 years (range: 8–59 years), with disease duration of 137.9±124.8 months. The male to female ratio was 1:2.6 (11/29). The mode of onset was acute in 19.4%, subacute in 45.2% and chronic in 35.5%. Clinical courses were monophasic in 10 (26.3%), relapsing remitting in 20 (52.6%) and chronic progressive in 8 (21.1%)

Table 1 Demographic features of 40 patients with CCPD

Basic demographics	N=40
Sex ratio (male/female)	11:29
Age at onset (years, mean±SD)	31.7±14.1
Age at examination (years, mean±SD)	36.5±14.6
Follow-up period (months, mean±SD)*	93.0±91.8
Disease duration (months, mean±SD)*	137.9±124.8
Mode of onset	n/N (%)
Acute	6/31 (19.4)
Subacute	14/31 (45.2)
Chronic	11/31 (35.5)
Clinical course	n/N (%)
Monophasic	10/38 (26.3)
Relapse–remitting	20/38 (52.6)
Chronic progressive	8/38 (21.1)
Initial symptoms	n/N (%)
Related to CNS involvement	15/38 (39.5)
Related to PNS involvement	15/38 (39.5)
Simultaneous or sequential	8/38 (21.0)
Fulfilment of MS or CIDP criteria	n/N (%)
McDonald criteria for MS	27/40 (67.5)
EFNS/PNS definite criteria for CIDP	35/40 (87.5)
Symptoms and signs during the entire course	n/N (%)
Seizure†	3/40 (7.5)
Mental disturbance†	5/40 (12.5)
Visual disturbance†	19/40 (47.5)
Right	1/19 (5.3)
Left	8/19 (42.1)
Bilateral	10/19 (52.6)
Cranial nerve involvement (other than the optic nerves)	17/39 (43.6)
Motor weakness‡	37/40 (92.5)
Hemiplegia†	10/36 (27.8)
Paraplegia†	6/36 (16.7)
Weakness of 4 extremities§	24/36 (66.7)
Muscle atrophy§	11/40 (27.5)
Respiratory disturbance	3/40 (7.5)
Gait disturbance	31/39 (79.5)
Cerebellar ataxia†	10/38 (26.3)
Sensory disturbance	37/39 (94.9)
Half-body involvement†	5/37 (13.5)
Sensory level†	14/37 (37.8)
Glove and stocking type§	22/37 (59.4)
Other types	3/37 (8.1)
Deep tendon reflexes	
Hyporeflexia§	26/40 (65.0)
Normal	1/40 (2.5)
Hyper-reflexia†	9/40 (22.5)
Both hyporeflexia and hyper-reflexia	4/40 (10.0)
Pathological reflexes†	18/40 (45.0)
Sphincter disturbance†	18/38 (47.4)

*Two patients' data were missing.
†Symptoms derived from CNS involvement.
‡Detail of motor weakness in one patient was unknown.
§Symptoms derived from PNS involvement.
CCPD, combined central and peripheral demyelination; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CNS, central nervous system; n, number of involved cases; N, number of cases collated; MS, multiple sclerosis; PNS, peripheral nervous system.

cases. Four patients had antecedent infections, of which three had respiratory infections and one had an alimentary infection. Only one patient developed CCPD after a vaccination (details of the vaccination are unknown). In the present survey, 67.5% (27/40) of the patients with CCPD met the McDonald criteria[20] for MS, while 87.5% (35/40) fulfilled the EFNS/PNS definite criteria for CIDP.[19]

Neurological symptoms and signs

The initial symptoms related to CNS involvement, such as visual disturbance, hemiplegia and hemibody sensory disturbance, were observed in 15 cases (39.5%), those related to PNS involvement, such as weakness and sensory disturbance of four extremities, in 15 cases (39.5%), and those related to both CNS and PNS involvement (simultaneous or sequential occurrence) in 8 cases (21%). The most common symptom/sign during the entire course was sensory disturbance (94.9%), the second most common symptom/sign was motor weakness (92.5%) and the third was gait disturbance (79.5%). Visual disturbance was observed in nearly half of the patients, with approximately 50% exhibiting bilateral involvement. Overall, cranial nerves were affected in 30/40 (75%) cases and optic nerves were the most commonly affected (19/30, 63.3%; see online supplementary table). Hyporeflexia and hyper-reflexia were seen in 65% and 22.5%, respectively, while four patients had both, depending on what was examined. Pathological reflexes were found in 45% and sphincter disturbance was present in 47.4%. About one-fourth of the patients showed muscle atrophy and cerebellar ataxia. Mental disturbance, seizure and respiratory disturbance were only occasionally observed.

Laboratory findings of peripheral blood and cerebrospinal fluid

Increased C reactive protein levels were found in only 10.5% of the cases and none of the patients had abnormal glycated haemoglobin levels (table 2). Few patients had common autoantibodies. Antiaquaporin 4 (AQP4) antibodies were not detected in any of the patients, whereas antineurofascin155 antibodies were found in 5/11 (45.5%). Epstein-Barr virus, herpes simplex virus, varicella zoster virus and mycoplasma were negative in all examined cases. Cerebrospinal fluid (CSF) protein levels were increased in 82.5% of the cases, while pleocytosis was present in 27.5%, indicating albuminocytological dissociation in 57.5%. The CSF oligoclonal IgG band positivity rate was only 7.4% and an elevated IgG index was found in 18.5% of the cases.

Table 2 Laboratory findings in 40 patients with CCPD

	n/N (%)
Blood	
High HbA1c level	0/37 (0)
CRP level >1.0 mg/dL	4/38 (10.5)
Hyperthyroidism	1/37 (2.7)
Hypothyroidism	3/37 (8.1)
Rheumatoid factor	1/31 (3.2)
ANA ≥1:160	1/31 (3.2)
Anti-SS-A Ab	0/35 (0)
Anti-SS-B Ab	0/35 (0)
MPO-ANCA	1/27 (3.7)
PR3-ANCA	0/25 (0)
Anti-AQP4 Ab	0/29 (0)
Antiganglioside Ab	2/24 (8.3)
Antineurofascin155 Ab	5/11 (45.5)
Monoclonal gammopathy	1/28 (3.6)
CSF	
Amounts of protein >40 mg/dL	33/40 (82.5)
Cell counts >5/μL	11/40 (27.5)
Albuminocytological dissociation	23/40 (57.5)
OB	2/27 (7.4)
Increased IgG index level	5/27 (18.5)

Ab, antibodies; ANA, antinuclear antibody; AQP4, aquaporin 4; CCPD, combined central and peripheral demyelination; CRP, C reactive protein; CSF, cerebrospinal fluid; HbA1c, glycated haemoglobin; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; N, number of cases collated; N, number of involved cases; OB, oligoclonal IgG bands; PR3-ANCA, proteinase-3-antineutrophil cytoplasmic antibody.

Neuroimaging, VEP and NCS findings

Following MRI examination, cerebral, cerebellar, brainstem and optic nerve lesions were detected in 75%, 15%, 32.5% and 17.5%, respectively (table 3). Among cases with cerebral lesions, 36.7% had nine or more lesions. Large lesions (>3 cm in diameter) were observed in 25% and gadolinium (Gd)-enhanced lesions were found in only 17.5%. Spinal cord lesions were found in 30/40 (75%) and the lesions in 11 cases were Gd-enhanced. Longitudinally extensive spinal cord lesions (LESCLs), extending three or more vertebral segments, were present in 3/40 (7.5%). VEPs were abnormal in 15/21 patients (71.4%) and bilaterally observed in 53.3% of these. Based on neurological, MRI and VEP findings, the involvement of multiple affected CNS sites (either two or three sites among the brain, optic nerves and spinal cord) was found in 70% of

Table 3 MRI and VEP findings in 40 patients with CCPD

	n/N (%)
MRI	
Cerebral lesions	30/40 (75.0)
≤3	6/30 (20.0)
4–8	13/30 (43.3)
≥9	11/30 (36.7)
Gd-enhancement	7/40 (17.5)
Lesions larger than 3 cm	10/40 (25.0)
Cerebellar lesions	6/40 (15.0)
Gd-enhancement	2/40 (5.0)
Brainstem lesions	13/40 (32.5)
Gd-enhancement	3/40 (7.5)
Optic nerve lesions	7/40 (17.5)
Gd-enhancement	1/40 (2.5)
Spinal cord lesions	30/40 (75.0)
LESCLs	3/40 (7.5)
Gd-enhancement	11/40 (27.5)
VEPs	
Abnormal findings	15/21 (71.4)
Right	2/15 (13.3)
Left	5/15 (33.3)
Bilateral	8/15 (53.3)
Affected CNS sites	
Brain only	4/40 (10.0)
Optic nerves only	1/40(2.5)
Spinal cord only	7/40 (17.5)
Brain+optic nerves	5/40 (12.5)
Brain+spinal cord	13/40 (32.5)
Optic nerves+spinal cord	2/40 (5.0)
Brain+optic nerves+spinal cord	8/40 (20.0)

CCPD, combined central and peripheral demyelination; CNS, central nervous system; Gd, gadolinium; LESCLs, longitudinally extensive spinal cord lesions; N, number of cases collated; N, number of involved cases; VEPs, visual-evoked potentials.

Table 4 Abnormal findings of NCS in 40 patients with CCPD

	Total†	Median‡	Ulnar‡	Tibial‡	Sural‡
Motor nerve					
Decreased MCV	31/40 (77.5)	55/69 (79.7)	47/66 (71.2)	46/63 (73.0)	
Prolonged distal latency	21/40 (52.5)	31/67 (46.3)	28/62 (45.2)	22/59 (37.3)	
Decreased or absent CMAP	22/40 (55.0)	19/70 (27.1)	26/69 (37.7)	44/70 (62.9)	
Conduction block	11/40 (27.5)	20/64 (31.3)	22/61 (36.1)	20/59 (33.9)	
Temporal dispersion	16/40 (40.0)	23/67 (34.3)	27/64 (42.2)	23/58 (39.7)	
Prolonged F-wave latency	28/40 (70.0)	38/54 (70.4)	29/45 (64.4)	34/41 (82.9)	
Decreased F-wave occurrence	19/40 (47.5)	28/58 (48.3)	24/50 (48.0)	21/50 (42.0)	
Sensory nerve					
Decreased SCV	17/40 (42.5)	20/53 (37.7)	30/49 (61.2)		17/38 (44.7)
Decreased or absent SNAP	35/40 (87.5)	41/66 (62.1)	50/68 (73.5)		43/60 (71.7)

†Patients with indicated abnormalities in any one of the three nerves were regarded as abnormal (numbers of abnormal patients/total numbers of patients examined).
‡Numbers of abnormal nerves/total numbers of nerves examined.
CCPD, combined central and peripheral demyelination; CMAP, compound muscle action potential; MCV, motor nerve conduction velocity; NCS, nerve conduction study; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential.

patients with CCPD, while isolated involvement of the brain, optic nerve lesions or spinal cord was present in 10%, 2.5% and 17.5%, respectively. Devic type (optic-spinal) involvement was observed in only 5%. In motor NCS, decreased motor nerve conduction velocity and prolonged F-wave latency were the most common findings, and were observed in 77.5% and 70% of patients with CCPD, respectively (table 4). Abnormal compound muscle action potential amplitude, prolonged distal latency and decreased F-wave occurrence were detected in approximately half of the patients. Conduction block and temporal dispersion were detected in 27.5% and 40%, respectively. In sensory NCS, decreased or absent sensory nerve action potential was recognised in as much as 87.5%, while decreased sensory nerve conduction velocity was present in 42.5%.

Treatment and prognosis

Patients with CCPD were most commonly treated with either intravenous or oral corticosteroids, followed by intravenous immunoglobulins, resulting in 83.3%, 75% and 66.7% improvement, respectively (table 5). Plasmapheresis was performed in only eight patients, of whom seven (87.5%) improved. By contrast, interferon-β (IFN-β) was effective in only one patient and the disease was actually exacerbated in three patients. At the illness peak, 16/40 (40%) patients with CCPD had severe disability, with a Hughes functional scale score of 4 or more, and three required artificial ventilation (figure 1). However, after treatment, 26 of 40 (65%) patients had no or only mild disabilities (≤1 Hughes functional scale score).

Table 5 Treatment response in 40 patients with CCPD

Treatment	Efficacy n/N (%)
Corticosteroid pulse therapy*	30/36 (83.3)
Oral corticosteroids	21/28 (75.0)
IVIg	18/27 (66.7)
Plasmapheresis	7/8 (87.5)
IFN-β	1/10 (10.0)

*500 mg/day for three consecutive days were administered to two patients, while 1000 mg/day for three consecutive days were administered to the remaining patients.
CCPD, combined central and peripheral demyelination; IFN-β, interferon β; IVIg, intravenous immunoglobulin; N, number of cases collated; n, number of efficacious cases.

Comparison of clinical features between patients with CCPD with simultaneous or temporarily separated onset of CNS and PNS involvement

We classified the collated patients into two subgroups according to the pattern of onset: simultaneous or sequential involvement of both CNS and PNS at onset (simultaneous onset group), or temporarily separated onset of CNS and PNS involvement (temporarily separated onset group). Follow-up period and disease duration were significantly shorter in the simultaneous onset group than in the temporarily separated onset group (44.6 ±45.0 months vs 112.0±97.7 months, p=0.0316 and 56.9 ±58.2 vs 169.3±128.5 months, p=0.0055, respectively; table 6). In the temporarily separated onset group, patients who had already been diagnosed as MS when PNS demyelination developed were seen in 9/15 (60%), while those who had already been diagnosed as CIDP when CNS demyelination developed were seen in 7/15 (46.7%) cases. The Hughes functional scale scores at the peak of illness were significantly greater in the simultaneous onset group than the temporarily separated onset

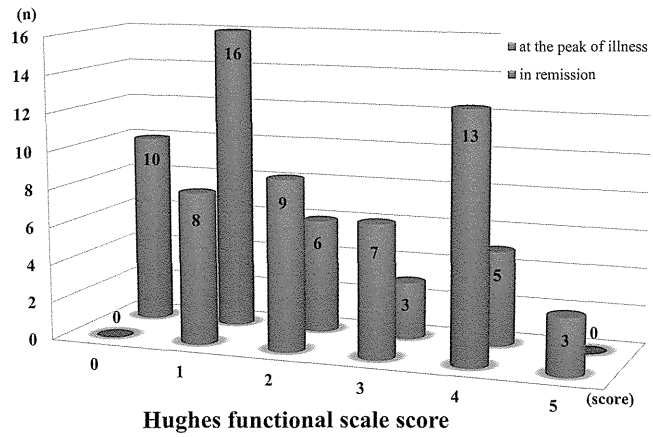

Figure 1 Hughes functional scale scores at the peak of illness and in remission. Forty patients with combined central and peripheral demyelination were evaluated by the Hughes functional scale score at the peak of illness and in remission. No one died because of the disease. The post-treatment scores became significantly less than the pretreatment scores (2.85±1.29 to 1.43±1.30, p<0.0001). All three patients with grade 5 at the peak of illness belonged to the simultaneous onset group.

Table 6 Comparison of clinical features between patients with CCPD with simultaneous or temporarily separated onset of CNS and PNS involvement*

	Temporarily separated onset group	Simultaneous onset group	p Value†
Demographics	N=30	N=8	
Sex ratio (male/female)	7:23 (1:3.3)	2:6 (1:3)	NS
Age at onset (years, mean±SD)	29.4±13.2	35.0±14.9	NS
Age at examination (years, mean±SD)	35.5±14.8	36.0±14.1	NS
Follow-up period (months, mean±SD)‡	112.0±97.7	44.6±45.0	0.0316
Disease duration (months, mean±SD)‡	169.3±128.5	56.9±58.2	0.0055
Mode of onset	n/N (%)	n/N (%)	
Acute	4/22 (18.2)	2/8 (25.0)	NS
Subacute	9/22 (40.9)	4/8 (50.0)	NS
Chronic	9/22 (40.9)	2/8 (25.0)	NS
Clinical course	n/N (%)	n/N (%)	
Monophasic	3/29 (10.3)	6/8 (75.0)	0.0008
Relapsing–remitting	19/29 (65.5)	1/8 (12.5)	0.0140
Chronic progressive	7/29 (24.1)	1/8 (12.5)	NS
Fulfilment of MS or CIDP criteria	n/N (%)	n/N (%)	
McDonald criteria for MS	22/30 (73.3)	4/8 (50.0)	NS
EFNS/PNS definite criteria for CIDP	26/30 (86.7)	7/8 (87.5)	NS
The number of patients who had already been diagnosed as MS when PNS demyelination developed	9/15 (60.0)		
The number of patients who had already been diagnosed as CIDP when CNS demyelination developed	7/15 (46.7)		
Hughes functional scale score	N=30	N=8	
At the peak of illness	2.73±1.14	3.75±1.39	0.0457
In remission	1.43±1.28	1.50±1.60	NS
Score changes after treatment	1.30±0.99	2.25±1.16	0.0427
Symptoms and signs	n/N (%)	n/N (%)	
Visual disturbance	19/30 (63.3)	0/8 (0.0)	0.0015
Cranial nerve involvement (other than optic nerves)	12/29 (41.4)	5/8 (62.5)	NS
Motor weakness	29/30 (96.7)	7/8 (87.5)	NS
Muscle atrophy	9/30 (30.0)	2/8 (25.0)	NS
Respiratory disturbance	0/30 (0.0)	3/8 (37.5)	0.0066
Gait disturbance	22/29 (75.9)	7/8 (87.5)	NS
Cerebellar ataxia	8/30 (26.7)	2/6 (33.3)	NS
Sensory disturbance	30/30 (100.0)	5/7 (71.4)	0.0315
Pathological reflexes	13/30 (43.3)	5/8 (62.5)	NS
Sphincter disturbance	14/29 (48.3)	3/7 (42.9)	NS
Blood	n/N (%)	n/N (%)	
Antineurofascin 155 Ab	3/8 (37.5)	2/3 (66.7)	NS
CSF	N=30	N=8	
Amounts of protein	85.3±64.9	126.5±88.3	NS
Cell counts	4.61±6.06	26.0±52.3	NS
	n/N (%)	n/N (%)	
Amounts of protein >40 mg/dL	24/30 (80.0)	7/8 (87.5)	NS
Cell counts >5/μL	7/30 (23.3)	3/8 (37.5)	NS
OB	2/21 (9.5)	0/5 (0.0)	NS
Increased IgG index level	4/20 (20.0)	1/6 (16.7)	NS
MRI	n/N (%)	n/N (%)	
Brain lesions	23/30 (76.7)	8/8 (100.0)	NS
Cerebral lesions	21/30 (70.0)	8/8 (100.0)	NS
Lesions more than 3 cm	5/30 (16.7)	5/8 (62.5)	0.0186
Cerebellar lesions	6/30 (20.0)	0/8 (0.0)	NS
Brainstem lesions	10/30 (33.3)	2/8 (25.0)	NS
Optic nerve lesions	6/30 (20.0)	1/8 (12.5)	NS
Spinal cord lesions	24/30 (80.0)	4/8 (50.0)	NS
LESCLs	0/30 (0.0)	3/8 (37.5)	0.0066
VEPs	n/N (%)	n/N (%)	
Abnormal VEP findings	14/17 (82.4)	1/4 (25.0)	0.0526§
Affected CNS sites	n/N (%)	n/N (%)	
Brain only	1/30 (3.3)	3/8 (37.5)	0.0237
Optic nerves only	1/30 (3.3)	0/8 (0.0)	NS
Spinal cord only	6/30 (20.0)	0/8 (0.0)	NS
Brain+optic nerves	4/30 (13.3)	1/8 (12.5)	NS
Brain+spinal cord	9/30 (30.0)	3/8 (37.5)	NS
Optic nerves+spinal cord	2/30 (6.7)	0/8 (0.0)	NS
Brain+optic nerves+spinal cord	7/30 (23.3)	1/8 (12.5)	NS
Treatment efficacy	n/N (%)	n/N (%)	
Corticosteroid pulse therapy	25/27 (92.6)	6/8 (75.0)	NS
Oral corticosteroids	17/20 (85.0)	4/6 (66.7)	NS
IVIg	13/20 (65.0)	4/5 (80.0)	NS
Plasmapheresis	5/6 (83.3)	2/2 (100.0)	NS

*Two patients were excluded because their patterns of onset were undetermined.
†A p value<0.05 is regarded as significant. Qualitative variables were analysed by Fisher exact test. Continuous variables that follow a parametric distribution were analysed by Student's t test, while non-parametric variables were analysed by Mann-Whitney U test.
‡Two patients' data in the temporarily separated onset group were missing.
§Indicates a trend (ie, p<0.1).
Ab, antibodies; CCPD, combined central and peripheral demyelination; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CNS, central nervous system; CSF, cerebrospinal fluid; IFN-β, interferon β; IVIg, intravenous immunoglobulin; LESCLs, longitudinally extensive spinal cord lesions; MS, multiple sclerosis; N, number of cases collated; n, number of involved cases; NS, not significant; OB, oligoclonal IgG bands; PNS, peripheral nervous system; VEPs, visual-evoked potentials.

group (2.73±1.14 vs 3.75±1.39, p=0.0457). The monophasic course was more frequently observed in the simultaneous onset group than the temporarily separated onset group (75% vs 10.3%, p=0.0008), whereas the relapsing–remitting course was more common in the temporarily separated onset group than the simultaneous onset group (65.5% vs 12.5%, p=0.0140). Visual disturbance and sensory disturbance were more commonly present in the temporarily separated onset group than the simultaneous onset group (63.3% vs 0%, p=0.0015 and 100% vs 71.4%, p=0.0315, respectively), while respiratory disturbance occurred more often in the simultaneous onset group than in the temporarily separated onset group (37.5% vs 0%, p=0.0066). On MRI, cerebral lesions >3 cm and LESCLs were more frequently found in the simultaneous onset group than in the temporarily separated onset group (62.5% vs 16.7%, p=0 0.0186, and 37.5% vs 0%, p=0.0066, respectively). For the CNS affected sites, there were significantly more patients with PNS involvement and isolated brain involvement in the simultaneous onset group than in the temporarily separated onset

group (37.5% vs 3.3%, p=0.0237). By contrast, no patients in the simultaneous onset group had PNS involvement and isolated spinal cord involvement, while six patients in the temporarily separated group showed PNS and isolated spinal cord involvement. Abnormal VEPs tended to be more frequently detected in the temporarily separated onset group than in the simultaneous onset group (82.4% vs 25%, p=0.0526). The Hughes functional scale scores were significantly lower following immunotherapies compared with pretreatment scores in the temporarily separated onset group and the simultaneous onset group (2.73 ±1.14 to 1.43±1.28, p=0.0002, and 3.75±1.39 to 1.50±1.60, p=0.0203, respectively). However, the improvement in these scores was more remarkable in the simultaneous onset group than in the temporarily separated onset group (2.25±1.16 vs 1.30±0.99, p=0.0427; figure 2). Even when we excluded the patient with a history of vaccination, we obtained essentially the same results, although the difference in the Hughes grade scores at the peak, and the score changes after treatment between the temporarily separated onset group and the simultaneous onset group, were no longer statistically significant because of the smaller sample size (data not shown).

DISCUSSION

CCPD is an extremely rare and devastating disease. We identified 40 patients throughout Japan during the study period. The numbers of registered MS and patients with CIDP in Japan in 2011 were 16 140 and 2986, respectively.[22] Even taking into consideration the response rates (50.3% in the first survey and 94.7% in the second), patients with CCPD were a very minor population (84 at most) among those with idiopathic demyelinating disorders (likely less than 0.52% of MS and 2.8% of patients with CIDP in Japan). The present nationwide survey is valuable for determining the characteristic features of CCPD. However, the study had some limitations. Many neurologists answered the questionnaires before the CCPD diagnostic criteria were established. In addition, because there are no specific biomarkers for either MS or CIDP, we could not differentiate these conditions from CCPD; instead, the number of patients who eventually met either the established MS or CIDP criteria was indicated. Nevertheless, the present study analysing the largest number of patients with CCPD defined by the same criteria is significant.

According to results from this study, CCPD was found in a preponderance of females and young adults. However, the age of onset ranged from 8 to 59 years, suggesting CCPD occurrence in a wide age range, except for elderly people. Thus, the ages of onset for CCPD overlap with those for MS and CIDP. Subacute or chronic onset was observed more often than acute onset, while a relapsing remitting or chronic progressive course was more common than a monophasic course. This suggested that a persisting inflammation affecting both the CNS and PNS was the main form of the disease. Indeed, most patients with CCPD reported in the literature to date show a relapsing remitting or chronic progressive course.[4–6 8–11 13–16] Initial symptoms that related to either CNS or PNS involvement were equally observed. CCPD had very high frequencies of motor weakness (>90%), as well as sensory disturbance with various distributions. Cranial nerve involvement that included optic nerves was also commonly seen in CCPD (75%).

The presence of widespread peripheral demyelination, as revealed by NCS and high frequency of albuminocytological dissociation, is compatible with CIDP. The abundant discrete CNS lesions which include the optic nerves and spinal cord on MRI are consistent with MS. However, several features distinct from

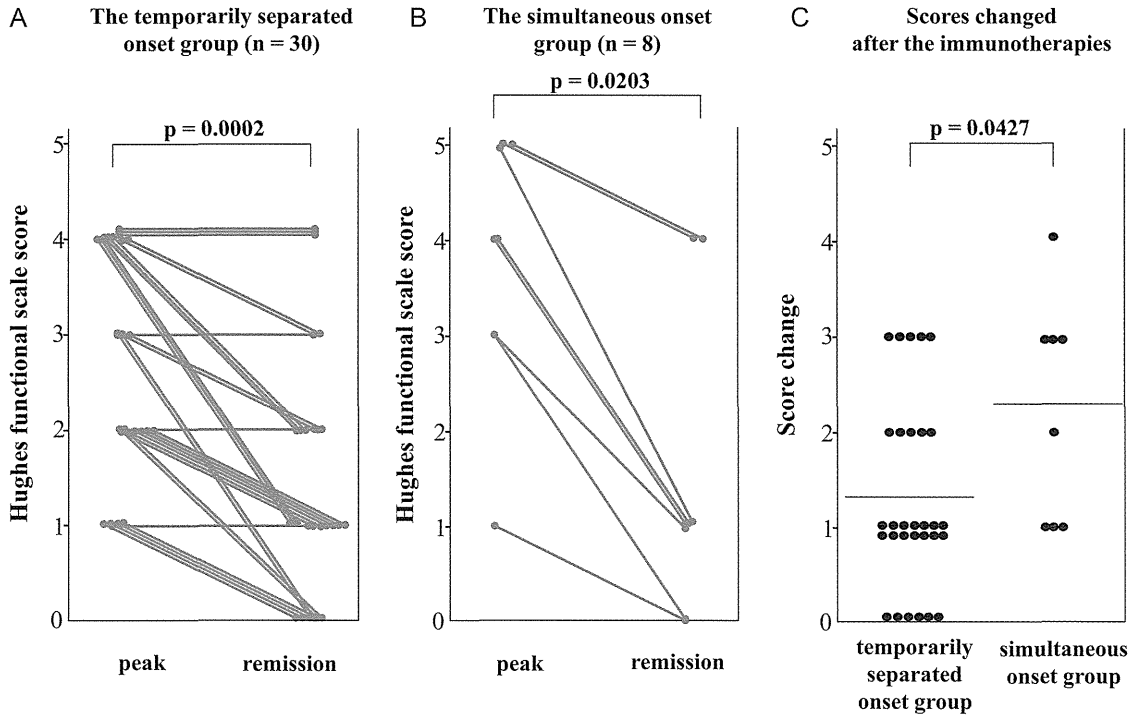

Figure 2 Comparison of treatment response in patients with combined central and peripheral demyelination with temporarily separated onset and those with simultaneous onset of central nervous system; and peripheral nervous system involvement. CCPD Hughes functional scale scores were significantly lower after immunotherapies compared with pretreatment scores in the temporarily separated onset group and simultaneous onset group (2.73±1.14 to 1.43±1.28, p=0.0002 and 3.75±1.39 to 1.50±1.60, p=0.0203, respectively). By contrast, score changes were more prominent in the simultaneous onset group than in the temporarily separated onset group (2.25±1.16 vs 1.30±0.99, p=0.0427). n=30 in the temporarily separated onset group and n=8 in the simultaneous onset group.