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Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients

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Summary

Paraneoplastic cerebellar degeneration (PCD) is a heterogeneous group of disorders characterized by subacute cerebellar ataxia, specific tumour types and (often) associated antineuronal antibodies. Nine specific antineuronal antibodies are associated with PCD. We examined the relative frequency of the antineuronal antibodies associated with PCD and compared the neurological symptoms and signs, associated tumours, disability and survival between groups of PCD with different antibodies. Also, we attempted to identify patient-, tumour- and treatment-related characteristics associated with functional outcome and survival. In a 12-year period, we examined >5000 samples for the presence of antineuronal antibodies. A total of 137 patients were identified with a paraneoplastic neurological syndrome and high titre (≥400) antineuronal antibodies. Fifty (36%) of these patients had antibody-associated PCD, including 19 anti-Yo, 16 anti-Hu, seven anti-Tr, six anti-Ri and two anti-mGluR1. Because of the low number, the anti-mGluR1 patients were excluded from the statistical analysis. While 100% of patients with anti-Yo, anti-Tr and anti-mGluR1 antibodies suffered PCD, 86% of anti-Ri and only 18% of anti-Hu patients had PCD. All patients presented with subacute cerebellar ataxia progressive over weeks to months and stabilized within 6 months. The majority of patients in all antibody groups had both truncal and appendicular ataxia. The frequency of nystagmus and dysarthria was lower in anti-Ri patients (33 and 0%). Later in the course of the disease, involvement of non-cerebellar structures occurred most frequently in anti-Hu patients (94%). In 42 patients (84%), a tumour was detected. The most commonly associated tumours were gynaecological and breast cancer (anti-Yo and anti-Ri), lung cancer (anti-Hu) and Hodgkin's lymphoma (anti-Tr and anti-mGluR1). In one anti-Hu patient, a suspect lung lesion on CT scan disappeared while the PCD evolved. Seven patients improved by at least 1 point on the Rankin scale, while 16 remained stable and 27 deteriorated. All seven patients that improved received antitumour treatment for their underlying cancer, resulting in complete remission. The functional outcome was best in the anti-Ri patients, with three out of six improving neurologically and five were able to walk at the time of last follow-up or death. Only four out of 19 anti-Yo and four out of 16 anti-Hu patients remained ambulatory. Also, survival from time of diagnosis was significantly worse in the anti-Yo (median 13 months) and anti-Hu (median 7 months) patients compared with anti-Tr (median >113 months) and anti-Ri (median >69 months). Patients receiving antitumour treatment (with or without immunosuppressive therapy) lived significantly longer [hazard ratio (HR) 0.3; 95% confidence interval (CI) 0.1–0.6; *P* = 0.004]. Patients ≥60 years old lived somewhat shorter from time of diagnosis, although statistically not significant (HR 2.9; CI 1.0–8.5; *P* = 0.06).

Keywords: autoantibodies; paraneoplastic; cerebellar ataxia; cancer; immunotherapy

Abbreviations: Ab = antibody; CR = complete remission; OS = overall survival; PCD = paraneoplastic cerebellar degeneration; PEM/SN = paraneoplastic encephalomyelitis/sensory neuropathy; PNS = paraneoplastic neurological syndrome; RS = Rankin scale; SCLC = small cell lung carcinoma

Introduction

Subacute cerebellar ataxia in a patient with a known cancer is often due to metastatic invasion or other complications of the cancer, such as infection, coagulopathy, metabolic and nutritional deficits or side effects of treatment (Henson and Urich, 1982). When tumour- and treatment-related causes have been excluded, the patient is considered to suffer from paraneoplastic cerebellar degeneration (PCD). In adult patients who are not known to have a malignancy, subacute cerebellar ataxia may cause a diagnostic challenge, as PCD can precede the presentation of a neoplasm by several months to years (Posner, 1995). In these patients, the detection of high titre antineuronal autoantibodies directed against onconeural antigens establishes the diagnosis of PCD and directs the search towards an underlying neoplasm (Table 1).

Brouwer first described PCD in 1919 (Brouwer, 1919), but the association of cerebellar ataxia and cancer was not recognized until 1938 (Brouwer and Biemond, 1938). Ovarian, lung and breast cancer and Hodgkin's lymphoma are the neoplasms most commonly associated with PCD (Henson and Urich, 1982). The pathology of PCD is characterized by severe loss of cerebellar Purkinje cells and the presence of inflammatory infiltrates in affected areas of the nervous system (Henson and Urich, 1982). Trotter *et al*. (1976) first described autoantibodies reactive with cerebellar Purkinje cells in the serum of a patient with Hodgkin's lymphoma and PCD. Since then, the search for paraneoplastic antineuronal antibodies (Abs) associated with PCD has resulted in the identification of many paraneoplastic Abs and the subsequent cloning of their onconeural target antigens (Table 1). PCD represents a heterogeneous group of related disorders that differ in their clinical features, prognosis, associated neoplasms and type of paraneoplastic Abs (Posner, 1995).

We reviewed 137 subjects with a definite, Ab-associated, paraneoplastic neurological syndrome (PNS) in order to determine the relative frequency of PCD. We subsequently studied the 50 identified PCD patients to compare neurological signs and symptoms, associated tumours, disability and survival between groups of patients with different Abs. In addition, we attempt to identify patient-, tumour- and treatment-related characteristics associated with neurological disability and survival.

Methods

Immunological studies

In a 12-year period (1989–2001), we examined serum and CSF samples from ~5000 patients. Physicians who suspected that their patients suffered from PNS had submitted the patient samples to our laboratory for determination of paraneoplastic antineuronal Abs. During the entire study period, all samples were screened on rat frozen cerebellar sections using indirect immunofluorescence (Moll *et al*., 1993). All positive sera were confirmed by western blotting, using rat cerebellar extract (Moll *et al*., 1993; Honnorat *et al*., 1998) and purified recombinant HuD, CDR62, amphiphysin and NOVA-1 antigens (Fathallah-Shaykh *et al*., 1991; Buckanovich *et al*., 1993; De Camilli *et al*., 1993; Manley *et al*., 1995). Anti-Tr was diagnosed by strict immunohistochemical criteria when Purkinje cell cytoplasmic staining was combined with a characteristic punctuated staining of Purkinje cell dendrites (Graus *et al*., 1998). Anti-mGluR1 was confirmed by reactivity with mGluR1-expressing Chinese hamster ovary (CHO) cells (Sillevis Smitt *et al*., 2000). Titration was performed by indirect immunofluorescence, and titres were reported as the reciprocal of the highest dilution yielding clearly positive staining. Only sera with specific staining patterns at titres $\geqslant$400 combined with reactivity with purified onconeural fusion protein were considered in this study. Patients were considered affected by PCD when they presented with cerebellar ataxia not attributable to metastases, infection, metabolic, hereditary, toxic or iatrogenic causes combined with the detection of high titre ($\geqslant$400) antineuronal Ab.

Subjects

We have identified a total of 137 patients with high titre antineuronal Abs. Fifty (36%) of these patients had PCD, including 19 anti-Yo, 16 anti-Hu, seven anti-Tr, six anti-Ri and two anti-mGluR1 (Table 2). While 100% of patients with anti-Yo, anti-Tr or anti-mGluR1 Abs suffered PCD, 86% of anti-Ri and only 18% of anti-Hu patients had PCD. None of the patients with anti-amphiphysin or anti-CV2 Abs in our series presented with PCD. Fourteen of the 50 PCD patients were seen at the Erasmus University Medical Centre Rotterdam, and the hospital charts of these patients were reviewed. Samples from the other 36 patients had been submitted by physicians, mostly from The Netherlands and Belgium, and clinical information was obtained from review of the case records sent to us by their outside medical specialists. Follow-up information was obtained from the patients' general practitioners.

Patient information was reviewed for neurological signs and symptoms at presentation and after stabilization of the syndrome. CNS dysfunction was classified as cerebellar degeneration, limbic encephalitis, brainstem encephalitis or myelitis. Cerebellar signs and symptoms were classified further as ataxia (predominantly truncal, appendicular or both), nystagmus and dysarthria. Signs and symptoms of peripheral nervous system dysfunction were classified as peripheral neuropathy (sensory, mixed somatic, autonomic or motor neuronopathy), focal neuropathy or radiculopathy. Fifty patients with predominantly cerebellar symptoms and signs at presentation were identified (Table 2).

The neurological disability was scored using a modified Rankin scale (RS) (Graus *et al*., 1992; Keime-Guibert *et al*., 1999) at the time of diagnosis (first positive antineuronal Ab result), before onset of treatment and at last follow-up. On the modified RS, a score of 0 represents an asymptomatic patient;

Table 1 *Paraneoplastic antibodies in PCD*

Antibody	Clinical syndromes	Immunohistochemistry	Western blot cerebellar extract	Gene	Associated cancer	Reference
Anti-Yo	Cerebellar ataxia	Cytoplasm of Purkinje cells and large brainstem neurons	34, 52 and 62 kDa	cdr34, cdr62-1, cdr62-2	Ovarian, breast	Fathallah-Shaykh *et al.* (1991); Peterson *et al.* (1992)
Anti-Hu	Cerebellar ataxia, PEM/SN	Nuclei of all neurons, nucleolar sparing	35–40 kDa	HuD, HuC, Hel-N1	SCLC	Szabo *et al.* (1991); Dalmau *et al.* (1992)
Anti-Ri	Cerebellar ataxia, OM	Nuclei of all central neurons, with nucleolar sparing	55 and 80 kDa	NOVA-1, NOVA-2	Breast, gynaecological, SCLC	Luque *et al.* (1991); Buckanovich *et al.* (1993)
Anti-Tr	Cerebellar ataxia	Cytoplasm and dendrites of Purkinje cells	–	Unknown	Hodgkin's lymphoma	Graus *et al.* (1997, 1998)
Anti-VGCC	Cerebellar ataxia, LEMS	–	–	CACNA1A	SCLC (60%)	Mason *et al.* (1997)
Anti-Ma	Cerebellar ataxia, brainstem dysfunction	Nuclei and cytoplasm of neurons	37 and 40 kDa	Ma1-5	Many	Dalmau *et al.* (1999)
Anti-Ta/Ma2	Limbic encephalopathy, cerebellar ataxia	Nuclei and cytoplasm of neurons	40 kDa	Ma2	Testis	Voltz *et al.* (1999)
Anti-CRMP5/CV2	PEM/SN, cerebellar ataxia	Cytoplasm of oligodendrocytes	66 kDa	CRMP5	SCLC, thymoma, gynaecological	Honnorat *et al.* (1996, 1999)
Anti-mGluR1	Cerebellar ataxia	Cytoplasm of Purkinje cells and brush cells, climbing fibres	–	MGluR1	Hodgkin's lymphoma	Sillevis Smitt *et al.* (2000)

OM = opsoclonus/myoclonus; VGCC = voltage-gated calcium channels; LEMS = Lambert–Eaton myasthenic syndrome.

Table 2 *Main clinical syndromes at presentation and high titre (⩾400) paraneoplastic antineuronal autoantibodies detected over a 12-year period (1989–2001)*

Antibody	*n*	PCD (%)	PSN	PLE	PEM	POM	SPS
Anti-Hu	90	16 (18)	46	14	13	1	–
Anti-Yo	19	19 (100)	–	–	–	–	–
Anti-Tr	7	7 (100)	–	–	–	–	–
Anti-Ri	7	6 (86)	–	–	–	1	–
Anti-amphiphysin	7	–	4	1	1	–	1
Anti-CV2	5	–	3	1	1	–	–
Anti-mGluR1	2	2 (100)	–	–	–	–	–
Total	137	50 (37)	53	16	15	2	1

PSN = paraneoplastic sensory neuropathy; PLE = paraneoplastic limbic encephalitis; PEM = paraneoplastic encephalomyelitis; POM = paraneoplastic opsoclonus/myoclonus; SPS = stiff person syndrome.

1, symptoms that do not interfere with lifestyle; 2, symptoms that lead to some restriction of lifestyle but do not prevent totally independent existence; 3, symptoms that significantly interfere with lifestyle or prevent totally independent existence; 4, symptoms that clearly prevent independent existence, although the patient does not need constant attention; and 5, severe disability is present with total dependence requiring constant attention. A patient was considered neurologically improved or deteriorated if there was a change of at least 1 point in the RS score measured at the time of diagnosis (positive Ab test) or onset of the treatment compared with the RS score at the time of stabilization of the symptoms (Keime-Guibert *et al*., 2000).

Statistical analysis

Due to the low number, the two patients with anti-mGluR1-associated PCD were excluded from the statistical analysis, leaving 48 patients. End points included overall survival (OS) from date of diagnosis (anti-neuronal Ab) and functional outcome at stabilization. OS was calculated until the date of death from any cause. Patients still alive at the date of last contact were then censored. OS was estimated by the Kaplan–Meier method, and Kaplan–Meier curves of the four anti-neuronal Ab groups were compared using the log-rank test.

The following variables were included in the analysis of prognostic factors: type of anti-neuronal Ab, age at diagnosis (<59 versus ⩾60 years), presence of tumour, RS score at diagnosis (0–3 versus 4–5) and treatment (no treatment versus immunotherapy only versus antitumour treatment with or without immunotherapy).

Patient characteristics of the four antineural Ab groups were compared using Fisher's exact test in the case of discrete variables or the Kruskal–Wallis test in the case of continuous variables.

Univariate Cox regression analysis was used to detect differences in OS between subgroups. Univariate logistic regression was used to test for a difference in functional outcome between subgroups.

We used Spearman's rank correlation to test whether there was an association between RS score at diagnosis and the time between onset of neurological symptoms and the date of diagnosis.

All P values are two-sided, and a significance level $\alpha = 0.05$ was used. All statistical analyses were performed using Stata software (StataCorp. 2001, Stata Statistical Software: Release 7.0, Stata Corporation, College Station, TX) and GraphPad Prism version 3.0 software (GraphPad Software, Inc., San Diego, CA, 1999).

Results

Patient characteristics

Patient characteristics are summarized in Table 3. All patients presented with a subacute cerebellar syndrome that evolved over weeks to months and stabilized within 6 months. The patients in the anti-Tr group tended to be younger than those in the other groups, reflecting the different age distribution of the associated tumours, in particular Hodgkin's disease. However, this was not statistically significant ($P = 0.4$). The median interval between the onset of symptoms and definite diagnosis of PCD (defined by detection of specific Ab) varied slightly between 3.5 months (anti-Yo) and 6.0 months (anti-Hu) ($P = 0.9$). At the time of diagnosis of PCD, the majority of patients in all Ab groups suffered both truncal and appendicular ataxia. The frequency of nystagmus and dysarthria was lower in anti-Ri patients (33 and 0%) than in the anti-Yo (68 and 84%), anti-Hu (69 and 50%) and anti-Tr (86 and 86%) patients. In all patients, the predominant neurological syndrome at the time of PCD diagnosis was cerebellar ataxia. Many developed additional, non-cerebellar symptoms or signs (Table 3). Involvement of non-cerebellar structures occurred most frequently in anti-Hu patients, indicating that PCD associated with anti-Hu Abs represents a more diffuse paraneoplastic encephalomyelitis. Despite these differences, the RS score at the time of diagnosis did not differ significantly between the patient groups ($P = 0.6$).

Associated tumours

The associated tumours in the five patient groups are summarized in Table 4. A tumour was diagnosed in 42 of

Table 3 *Clinical characteristics of 48 PCD patients*

	Anti-Yo	Anti-Hu	Anti-Tr	Anti-Ri	Anti-mGluR1
No. of patients	19	16	7	6	2
F/M	19/0	4/12	1/6	5/1	2/–
Age at diagnosis (median, range) (years)	64 (37–79)	67 (51–79)	54 (29–73)	65 (52–76)	19, 50
Additional neurological symptoms:					
Peripheral neuropathy	–	8	–	–	–
Limbic encephalitis	–	4	1	1	1
Brainstem encephalitis	6	10	–	3	–
Opsoclonus/myoclonus	–	1	–	4	–
Myelitis	–	1	–	1	–
Isolated PCD	13	1	6	2	1
Median delay between symptoms and diagnosis (range)	3.5 (0.3–52.8)	6.0 (0.9–18.4)	4.8 (1.2–13.0)	5.2 (0.8–13.3)	0.5 (0.5–12)
No. of patients with tumour	15	14	6	5	2
PCD before tumour diagnosis	5	13	6	2	–
Median interval PCD to tumour diagnosis (range)	3.5 (0.3–52.8)	6.0 (0.9–18.4)	4.8 (1.2–13.0)	5.2 (0.8–13.3)	–
Median survival (months)	13	7	>113	>69	24
Cause of death*					
Neurological	8	6	1	1	–
Oncological	4	2	–	–	–
Unknown/unrelated	–	2	–	–	1

*Death was scored as oncological when the patient died from tumour progression and as neurological when the paraneoplastic process contributed directly to death (e.g. in brainstem encephalitis) or when the neurological disability was judged to be a major contributing factor to death (e.g. pneumonia in a bedridden patient).

Table 4 *Associated tumours in 50 PCD patients*

Antibody	*n*	Lung	Gynaecological	Breast	Hodgkin's	Other	No tumour
Anti-Yo	19	–	9	3	–	3	4
Anti-Hu	16	14	–	–	–	–	2
Anti-Tr	7	–	–	–	6	–	1
Anti-Ri	6	–	1	3	–	1	1
Anti-mGluR1	2	–	–	–	2	–	–
Total	50	14	10	6	8	4	8

50 PCD patients (84%). In 26 (62%) of these tumour patients, the PCD preceded the diagnosis of the tumour. In 10 of the 15 anti-Yo patients (67%) with a tumour, the PCD presented in patients already known to have a cancer. Nine of these patients had reached complete remission (CR) following initial antitumor treatment. In five, the PCD was shortly followed by tumour recurrence; in three, the tumour recurred prior to PCD; and two remained free of recurrent tumour. One patient died 3 months after onset of PCD, 2.5 years after reaching CR for ovarian cancer. At autopsy, no recurrent tumour was found and neuropathological examination demonstrated complete loss of Purkinje cells. The second patient developed PCD 22 months after reaching CR for ovarian cancer. At last follow-up, 2 years after onset of PCD, regular gynaecological examinations had not yet revealed a recurrence.

In eight patients, no tumour was demonstrated. Four anti-Yo patients had no detected tumour. Two of these patients were still alive at the time of last follow-up, 44 and 58 months from onset of symptoms. Of the two deceased patients, one had mildly elevated CA125 and weight loss. She probably had an underlying ovarian cancer that could not be demonstrated, and died 32 months after onset of symptoms. The second deceased patient was in a poor condition; the family declined an extensive work-up and she died 9 months after onset of PCD. Due to the limited work-up, an underlying malignancy has not been excluded.

Of the two anti-Hu patients without demonstrable tumour, one had a suspect adrenal lesion possibly representing an adrenal small cell lung carcinoma (SCLC) metastasis. This diagnosis was not pursued further because of the patient's poor clinical condition, and she died 10 months after the diagnosis of PCD in a nursing home. The other patient is a 58-year-old man with a long history of cigarette smoking who presented with a mainly appendicular ataxia. He subsequently developed a pancerebellar syndrome and brainstem signs. Anti-Hu Abs were tested positive 18 months after onset of symptoms. The patient remained ambulatory but could not

Table 5 *Neurological outcome in 50 PCD patients*

Functional status	Anti-Yo	Anti-Hu	Anti-Tr	Anti-Ri	Anti-mGluR1	All patients
No. of patients	19	16	7	6	2	50
At diagnosis						
RS score <3	11	9	6	4	1	31
RS score ⩾4	8	7	1	2	1	19
Evolution RS score						
Improved (⩾1 point)	1	1	1	3	1	7
Stable	4	7	3	1	1	16
Deterioration (⩾1 point)	14	8	3	2	–	27
At plateau						
RS score <3	4	4	3	5	1	17
RS score ⩾4	15	12	4	1	1	33

Table 6 *Neurological outcome by treatment in 50 PCD patients*

Treatment/outcome	Anti-Yo	Anti-Hu	Anti-Tr	Anti-Ri	Ant-mGluR1	All patients
No. of patients	19	16	7	6	2	50
Patients with tumour	15	14	6	5	2	42
Antitumour treatment	5	1	3	1	–	10
Improved/stable	–	1	2	–	–	3
Immunosuppression	4	5	–	3	2	14
Improved/stable	2	2	–	2	1	7
Both treatments	6	2	3	2	–	13
Improved/stable	2	2	2	2	–	8
No treatment	4	7	1	–	–	12
Improved/stable	2	4	–	–	–	6

Patients are considered improved or stable when the RS score from time of diagnosis of PCD did not deteriorate.

live independently. A CT scan demonstrated a suspect lesion in the left upper lobe. The lesion disappeared spontaneously and, at the time of last follow-up, 68 months after onset of the ataxia, the patient was alive without signs of cancer.

In one anti-Tr and one anti-Ri patient, no tumour was found. The anti-Tr patient died 10 months after PCD onset. At autopsy, no tumour was detected. The anti-Ri patient has remained free of cancer during 4.5 years of follow-up.

Neurological outcome

The neurological outcome is presented in Table 5. In general, at the time of neurological diagnosis, 63% of patients were ambulatory (RS score <3). When PCD had reached its plateau phase, only 34% were still able to walk. The functional outcome was significantly different between the four patient groups ($P = 0.04$). Outcome was worst in the anti-Yo patients (79% bedridden) followed by anti-Hu (75%), anti-Tr (57%) and anti-mGluR1 (50%) patients. The prognosis in the anti-Ri patients was much better, and 83% retained their ability to walk. Using logistic regression, age ⩾60 years [odds ratio (OR) 5.4; 95% confidence interval (CI) 1.4–21.2; $P = 0.02$] and a higher RS score at diagnosis (OR 3.8; 95% CI 0.9–16.1; $P = 0.07$) predicted worse functional outcome (RS 4–5). Neither immunotherapy (OR 0.4; 95% CI 0.1–2.8; $P = 0.4$) nor antitumour treatment (OR 0.3; 95% CI 0.1–2.0; $P = 0.3$) significantly affected functional outcome (Table 6). Seven patients (14%) improved neurologically from the time of diagnosis or start of treatment: three anti-Ri patients and one each with anti-Yo, anti-Hu, anti-Tr and anti-mGluR1 Abs (Table 7). Remarkably, all patients who improved neurologically received antitumour treatment, and CR was achieved in all. Patient 2 (Table 7) developed PCD shortly after diagnosis of a lymph node metastasis in the groin, probably from an ovarian cancer. At presentation, her RS score was 3 (ambulatory) but she deteriorated despite intravenous immunoglobulin G (IVIg) treatment and became bedridden (RS score = 4) prior to transfer to our hospital. After obtaining informed consent, she was treated with four cycles of rituximab (375 mg/m^2). After the first cycle, she regained her ability to walk (RS score = 3) and remained stable for >1 year. Rituximab (Roche Ltd, Basel, Switzerland) is a chimeric mouse–human anti-CD20 monoclonal Ab effectively used in the treatment of B-cell lymphomas (Maloney *et al*., 1994, 1997). Rituximab has also been effective in a variety of Ab-associated autoimmune disorders (Arzoo *et al*., 2002). In patient 2, the rituximab treatment eliminated circulating CD19$^+$ B cells but did not result in lower anti-Yo titres in serum (Table 7) or CSF. In the patients with anti-Tr and anti-mGluR1, the Abs had disappeared from the serum

Table 7 *Characteristics of seven PCD patients with improvement of functional status by at least 1 point on the modified Rankin scale*

No.	Antibody	Age	Tumour	Antitumour treatment	Immunosuppression	RSD	RSE	STD	STE
1	Anti-Hu	66	SCLC	CR	None	4	1	>1600	NA
2	Anti-Yo	47	Adenocarcinoma	CR	IVIg, rituximab	3*	3	6400	12 800
3	Anti-Tr	31	Hodgkin	CR	None	3	0	1600	Neg
4	Anti-Ri	58	Breast cancer	CR	PE, steroids, azathioprine	3	2	25 600	800
5	Anti-Ri	56	Tuba cancer	CR	Steroids	4	1	12 800	102 400
6	Anti-Ri	53	Breast cancer	CR	IVIg, steroids	4	2	3200	NA
7	Anti-mGluR1	19	Hodgkin	CR	IVIg, steroids, PE	3	0	3200	Neg

RSD = RS score at diagnosis; RSE = RS score at last follow-up; STD = serum antibody titre at diagnosis (IgG); STE = serum antibody titre after clinical improvement (IgG); NA = not available; Neg = negative; PE = plasma exchange. *This patient was diagnosed with PCD while still ambulatory (RSD = 3). She subsequently became bedridden (RS score = 4) despite treatment with IVIg. Following treatment with rituximab, she regained her ability to walk (RS score = 3) for > 1 year (see Results).

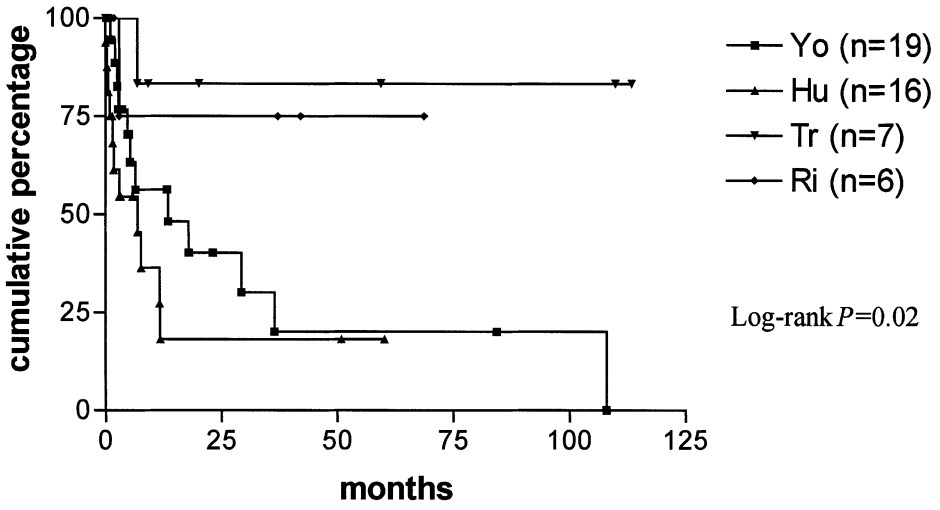

Fig. 1 Kaplan–Meier survival curves of 48 PCD patients with associated anti-Yo, anti-Hu, anti-Tr or anti-Ri antibodies.

at the time of clinical improvement (Table 7). In one of the anti-Ri patients, clinical improvement was paralleled by a decline in Ab titre, while high titres remained in the second anti-Ri patient despite neurological improvement. No follow-up serum was available from the third anti-Ri and the anti-Hu patients who had improved clinically.

Survival

The median survival of anti-Hu patients from time of diagnosis was 7 months, compared with 13 months in anti-Yo patients (Fig. 1). This difference in survival was statistically not significant [hazard ratio (HR) 1.7; 95% CI 0.7–3.9; P = 0.2]. Anti-Tr patients (median >113 months) lived significantly longer from time of first symptoms than anti-Yo (HR 0.12; 95% CI 0.02–0.97; P = 0.05) and anti-Hu patients (HR 0.13; 95% CI 0.02–1.00; P = 0.05). Anti-Ri patients (median >69 months) also lived longer than anti-Yo and anti-Hu patients, but the differences were not significant.

In patients ⩾60 years, there was a non-significant trend towards shorter survival from time of diagnosis (HR 2.9; 95% CI 1.0–8.5; P = 0.06). Patients receiving antitumour treatment (with or without immunosuppressive therapy) lived significantly longer (HR 0.3; 95% CI 0.1–0.6; P = 0.004). However, after adjustment for Ab group, there was no statistically significant treatment effect.

Discussion

We found that 36% of 137 patients with a definite PNS presented with subacute cerebellar ataxia, indicating that PCD is a common presentation of Ab-associated PNS. While anti-Hu was the most frequent paraneoplastic Ab detected in our study (66% of 137 patients), only 18% presented with PCD. In contrast, 100% of anti-Yo, anti-Tr and anti-mGluR1, and 86% of anti-Ri patients presented with PCD. In PCD patients, anti-Yo (38%) was detected most frequently, followed by anti-Hu (32%), anti-Tr (14%) and anti-Ri (12%) Abs. During the course of the disease, additional

non-cerebellar symptoms occurred most frequently in the anti-Hu patients (94%), indicating that PCD associated with anti-Hu Abs is part of a more widespread paraneoplastic encephalomyelitis/sensory neuronopathy (PEM/SN) (Dalmau *et al*., 1992; Graus *et al*., 2001; Sillevis Smitt *et al*., 2002).

The median age of the anti-Hu, anti-Yo and anti-Ri patients was 64–67 years and of the anti-Tr patients was 54 years. The latter median age is remarkable because all anti-Tr patients had associated Hodgkin's lymphoma. The age distribution of Hodgkin's lymphoma is bimodal, with an early peak in young adults and a second peak after age 50 (Gutensohn and Cole, 1980). Most anti-Tr and one of the anti-mGluR1 PCD patients belong to the second age peak, which may reflect a different mechanism in the pathogenesis of the Hodgkin's lymphoma between the two age groups.

Survival varied significantly between PCD patients with different Abs. The median survival from time of diagnosis in the anti-Hu patients was 7 and in anti-Yo patients 13 months, confirming the grim prognosis (Rojas *et al*., 2000; Graus *et al*., 2001; Sillevis Smitt *et al*., 2002). In contrast, the median survival in the anti-Tr (>117 months) and anti-Ri (>69 months) was not reached. Other factors predicting longer survival were administration of antitumour treatment and younger age.

In our study, 67% of the deceased anti-Yo patients died of a neurological cause, confirming two earlier reports (Hammack *et al*., 1990; Peterson *et al*., 1992). In contrast, Rojas *et al*. (2000) described death by a neurological cause in only 29% of anti-Yo patients, the majority dying from tumour progression. This difference is not explained by the associated malignancies. The most common associated tumours in anti-Yo patients were gynaecological (Hammack *et al*., 1990; Peterson *et al*., 1992; Rojas *et al*., 2000), in anti-Hu patients lung cancer (Dalmau *et al*., 1992; Graus *et al*., 2001; Sillevis Smitt *et al*., 2002), in anti-Tr and anti-mGluR1 patients exclusively Hodgkin's lymphoma (Graus *et al*., 1997), and in anti-Ri patients breast cancer (Luque *et al*., 1991). No tumour was detected in eight patients, while in one anti-Hu patient a radiologically suspect lung lesion disappeared spontaneously during the course of PCD. Remissions of radiologically suspect lung lesions and histologically confirmed SCLC during anti-Hu-associated PEM/SN have been reported previously (Darnell and DeAngelis, 1993; Zaheer *et al*., 1993) and support an important role for HuD-specific cytotoxic T lymphocytes (Benyahia *et al*., 1999; Plonquet *et al*., 2002).

In accordance with previous studies, 75% of anti-Hu patients became chair bound (Graus *et al*., 2001; Sillevis Smitt *et al*., 2002). Although symptoms were limited to the cerebellum in most, only 21% of the anti-Yo patients remained ambulatory, confirming previous reports of the grim neurological prognosis (Hammack *et al*., 1990; Peterson *et al*., 1992; Rojas *et al*., 2000). Neurological disability in anti-Tr and anti-mGluR1 was less severe, and 43 and 50% remained ambulatory, respectively. Anti-Ri PCD patients had the best neurological prognosis; 83% remained ambulatory and three out of six patients improved neurologically, confirming previous case reports (Dropcho *et al*., 1993; Jongen *et al*., 1998).

We studied factors which were involved in the neurological disability. We found that age $\geqslant$60 years and a higher RS score at diagnosis predicted worse functional outcome, while neither immunosuppression nor antitumour treatment had a significant effect. Larger studies have demonstrated better neurological outcome in patients receiving antitumour treatment for anti-Hu associated PEM/SN (Graus *et al*., 2001), while no such effect was demonstrated for anti-Yo-related PCD (Rojas *et al*., 2000). However, of the seven patients (14%) who improved neurologically, all had reached a CR of the tumour following antitumour treatment, and four had been treated additionally with some form of immunotherapy. One patient with anti-Yo-associated PCD regained her ability to walk following rituximab (anti-CD20) treatment. CD20 is a transmembrane surface antigen expressed only by B-cell precursors and mature B cells, and appears to play an important functional role in B-cell activation, proliferation and differentiation (Tedder and Engel, 1994). Rituximab is very effective in the treatment of B-cell lymphomas (Maloney *et al*., 1994, 1997) and it is used increasingly in the treatment of Ab-mediated autoimmune disorders including paraneoplastic pemphigus (Heizmann *et al*., 2001), myasthenia gravis (Zaja *et al*., 2000) and polyneuropathy associated with IgM Abs (Levine and Pestronk, 1999). Rituximab treatment results in long-lasting peripheral blood B-cell depletion, and we hypothesized that administration of rituximab would result in elimination of pre-B cells, preventing formation of new Ab-secreting cells and reducing anti-Yo titres not only in serum but also in CSF. Despite complete depletion of circulating $CD19^+$ B cells in our patient, her CSF and serum anti-Yo IgG titres remained high. Slight neurological fluctuations are common in anti-Yo-associated PCD, but a significant improvement rarely if ever occurs in this aggressive disorder (Peterson *et al*., 1992; Posner, 1995; Rojas *et al*., 2000), suggesting some role for rituximab in the neurological improvement in our patient. Although we do not fully understand the mechanism, rituximab treatment currently is under further evaluation. In three patients, the neurological improvement was paralleled by a decrease in Ab titre (one each with anti-Ri, anti-Tr and anti-mGluR1 Abs). In the anti-mGluR1 patient, the clinical improvement may have resulted directly from the disappearance of anti-mGluR1 from the serum because these autoantibodies have been shown to block the mGluR1 receptor *in vivo* (Sillevis Smitt *et al*., 2000). A pathogenic role for anti-Yo and anti-Hu Abs could never be proven in animal models (Graus *et al*., 1991; Sillevis Smitt *et al*., 1995), and demonstration of antigen-specific cytotoxic T lymphocytes in blood, CSF and target tissue (Benyahia *et al*., 1999; Albert *et al*., 2000; Plonquet *et al*., 2002) has shifted attention to a pathogenic role for the cellular immune response. Conventional immunosuppression is not effective in anti-Hu- and anti-Yo-associated PCD, and new treatment

modalities directed at a rapid destruction of the immune attack on the nervous system are warranted. Aggressive autoimmune disorders, including multiple sclerosis, are increasingly treated with haematopoietic stem cell transplantation following myelosuppressive conditioning (Burt *et al*., 1998; Fassas *et al*., 2002). In selected patients with an aggressive course of PCD, autologous haematopoietic stem cell transplantation may be considered in a carefully controlled protocol. In patients with a more indolent course and in patients with anti-Ri Abs, antitumour treatment and a trial of conventional immunotherapy is recommended.

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