

Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies

Article abstract—The outcome of 34 women with anti-Yo–associated paraneoplastic cerebellar degeneration was reviewed. Three patients had not developed cancer after more than 4 years of follow-up. The only independent predictor for survival was the type of associated tumor (risk ratio, 1.79; 95% CI, 1.02 to 3.12). Median survival was 100 months for patients with breast cancer and 22 for those with gynecologic cancer. Although paraneoplastic cerebellar degeneration leads to the diagnosis of cancer in 63% of the patients, cancer progression was the cause of death in 52%.

NEUROLOGY 2000;55:713–715

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Previous series and case reports have established the clinical characteristics and underlying neoplasms of patients with paraneoplastic cerebellar degeneration (PCD) associated with anti-Yo antibodies (Yo-Ab). The consensus is that the predictive value of Yo-Ab for the diagnosis of an underlying cancer is close to 100% and that patients can be cured from their tumor but remain severely disabled from the PCD. These assertions have been supported by clinical descriptions, usually with follow-up shorter than 2 years.^{1–3} In this study, we retrospectively analyzed the clinical outcome and prognostic factors in a series of 34 patients with PCD and Yo-Ab who were followed until death or for a median of 84 months.

Methods. Patients. We selected 34 patients with PCD and Yo-Ab from whom the following information was available: neurologic symptoms and degree of disability (Rankin score [RS]), type and stage of tumor, treatments given for the cancer and PCD, and cancer and neurologic outcomes. Follow-up was obtained through telephone calls and mail contact with the referring physicians. Yo-Ab were detected by immunohistochemistry on frozen sections of human cerebellum and confirmed by immunoblot of Yo recombinant protein as previously described.⁴

All 34 patients were women with a median age of 59 years (range, 29 to 72 years). At a median follow-up of 84 months (range, 16 to 165 months), 11 patients were alive (6) or lost to follow-up (5). All but five patients with known cancer received appropriate antineoplastic treatment. Tumor response was evaluated at the end of treatment by the patient's oncologist. Five patients were not treated: four were severely disabled and in one the tumor was diagnosed at autopsy. Twenty-three patients (67%) received

immunotherapy: plasmapheresis, immunoglobulins, corticosteroids, or cyclophosphamide either alone or in several combinations. Six patients were treated with chemotherapy and immunotherapy simultaneously. The neurologic disability was evaluated by a modified RS as previously reported.⁵ No patient improved with treatment of cancer or immunotherapy.

Statistical analysis. Survival time was determined from onset of PCD to death. Kaplan-Meier analysis was used to evaluate survival. Prognostic factors for survival were analyzed in the group of 25 patients with known cancer who received standard antineoplastic treatment. Differences between groups were estimated by log-rank test. A Cox proportional hazards regression model was used to verify associations of survival with several variables: age, tumor type (breast versus gynecologic), RS, time to reach the worst RS, first clinical diagnosis (PCD or tumor), and treatment with immunotherapy.

Results. Twenty patients (58.8%) were chairbound (RS >3) when PCD was diagnosed (median delay of diagnosis, 2 months); eventually, 32 patients (94%) became nonambulatory during the course of the disease. The time to reach the worst RS was less than 4 months in 65% of patients. Three patients had a less severe PCD and remained ambulatory (RS ≤3) for 8, 19, and 20 months.

Thirty patients had cancer (table 1). All 12 patients with breast cancer had metastatic lymph nodes at the time of tumor diagnosis. Two patients with negative mammograms had enlarged axillary lymph nodes that led to the discovery of the cancer. Fifteen of 18 patients with gynecologic cancer had metastatic disease; only three had a localized ovarian tumor that was detected after the diagnosis of PCD. Tumor was not found in four patients: one died 8 months after diagnosis of PCD and autopsy was not done, and the other three are alive with follow-ups of 49, 89, and 96 months.

PCD antedated the diagnosis of the tumor in 19 of 30 patients (63%) by a median of 5 months (range, 0 to 13 months). Five patients developed PCD shortly after starting cancer treatment and six after having completed treatment (median, 22 months; range, 6 to 43 months). One of these six patients developed PCD before a tumor recurrence, another at the time of tumor recurrence, and the other four died 3, 5, 11, and 15 months after developing PCD without clinical evidence of tumor relapse; however, periodic radiologic evaluations were not done and postmortem studies were not granted.

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F.G. is supported in part by grant SGR 9500027 Generalitat de Catalunya. I.R. is a recipient of a postresidency grant from the Ciutat Sanitaria Universitaria de Bellvitge, Hospitalet, Spain.

Received January 25, 2000. Accepted in final form May 9, 2000.

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Table 1 Clinical characteristics according to tumor type

Characteristic	Gynecologic (n = 18)*	Breast (n = 12)	Total
Temporal relation between PCD and tumor diagnosis			
PCD > 3 mo before tumor diagnosis	6	5	11
Simultaneous	8	5	13
PCD > 3 mo after tumor diagnosis	4	2	6
Staging at tumor diagnosis†			
Local	3	0	3
Regional (lymph nodes or adjacent structures)	7	10	17
Systemic metastases	5	1	6
No tumor	3	1	4
Immunotherapy	13	8	21
Response to tumor treatment			
Complete response	5	9	14
Other response	8	2	10
No treatment	5	0	5
Unknown	0	1	1
Median survival, mo	15	100	22
Cause of death			
Oncologic	9	3	12
Neurologic	6	2	8
Unknown	2	0	2

* Type of gynecologic cancer: ovary (13), fallopian tube (1), cervix (1), metastatic adenocarcinoma in the retroperitoneal lymph nodes (1), and pelvic tumor diagnosed by radiology (2).

† In two of the six patients who developed PCD when the tumor was in remission, staging refers to the time of tumor relapse. No tumor relapse was found in the other four patients.

PCD = paraneoplastic cerebellar degeneration.

The median survival of the 34 patients was 22 months (range, 3 to 164 months). The cause of death was related to tumor progression in 12 patients and to PCD in nine; and unknown in two. One patient with radiologic findings suggestive of a gynecologic cancer refused further studies or treatment and she was lost after a follow-up of 16 months.

In the 25 patients whose cancer was treated, the patient's age (60 years or older) and the presence of a gynecologic cancer were significantly associated with a shorter survival (table 2). The type of tumor was the only independent predictive factor for survival with a risk ratio of 1.79 (95% CI, 1.02 to 3.12). Median survival was 100 months for patients with breast cancer and 22 months for patients with gynecologic cancer. At the time of the analysis, all 13 patients with gynecologic cancer were dead and cancer progression was the cause of death in 61%. By contrast, 7 (58%) patients with breast cancer were alive (figure).

Discussion. We examined the long-term outcome of a series of 34 patients with PCD and Yo-Ab and found that, contrary to previous statements, the

Table 2 Association between clinical characteristics and survival in 25 patients with anti-Yo-antibody-positive PCD whose tumor was treated

Characteristic	Number	Median (range) survival, mo	p Value
Age, y			
<60	11	29 (12–164)	0.0335
≥60	14	15 (3–60)	
Tumor type			
Ovary	13	22 (3–41)	0.0068
Breast	12	100 (8–164)	
Rankin score at PCD diagnosis			
0–3	12	22 (5–60)	0.1483
4–5	13	28 (3–164)	
Time to worst Rankin score, mo			
≤3	14	26 (8–92)	0.9085
>3	11	15 (3–164)	
First event			
PCD	14	28 (8–93)	0.1827
Tumor	11	20 (3–164)	
Immunotherapy			
Yes	19	22 (3–164)	0.3024
No	6	38 (12–93)	

PCD = paraneoplastic cerebellar degeneration.

overall prognosis of the cancer is rather poor, particularly for patients with gynecologic tumors. Our finding is probably explained by two features. First, tumor progression was the main cause of death in 52% of the patients, even though PCD prompted the search of the tumor in 63% of the cases. Second, 29% of patients died as a result of the debilitating neurologic condition.

Our failure to cure the cancer in 52% of the patients is in part due to the fact that at the time of diagnosis most tumors had already metastasized to regional lymph nodes or extended beyond the initial organ. In our patients with gynecologic tumors, the frequency of limited disease was similar to the 17% found in a series of 18 patients with PCD and ovarian cancer.⁶ Although the gynecologic tumors of patients with PCD may have smaller volumes than those observed in patients without PCD,⁶ the detection of regional metastasis or invasion of local structures drastically decreases the possibility of tumor control.⁷ All our patients with breast cancer had axillary lymph node metastases, a feature that resembles the high frequency of regional (mediastinal) lymph node involvement in patients with small-cell lung cancer and anti-Hu-associated syndromes, suggesting that the tumor cells must invade the regional lymph nodes to trigger the immune response that causes the paraneoplastic neurologic disorder.⁸

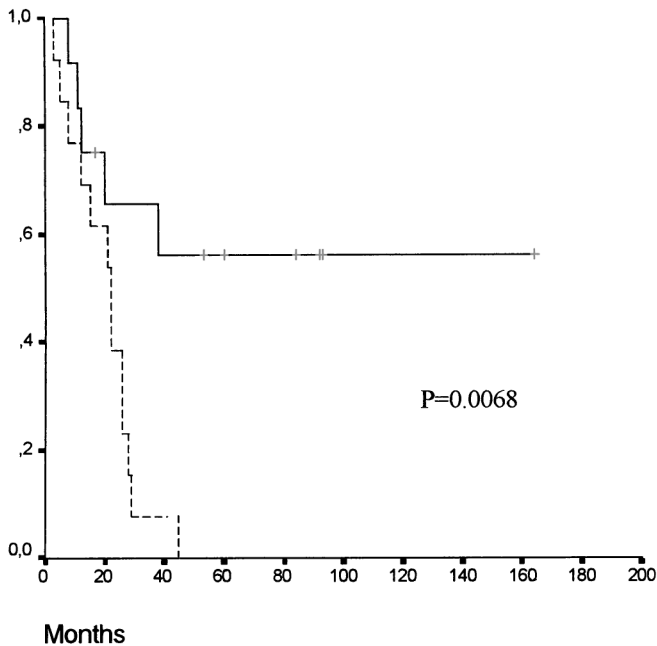


Figure. Kaplan-Meier survival curves for 25 patients with paraneoplastic cerebellar degeneration who received anti-neoplastic treatment. Solid line indicates breast cancer; dotted line, gynecologic cancer.

In patients with anti-Hu antibodies and paraneoplastic encephalomyelitis, effective treatment of the tumor appears to correlate with a stabilization of the neurologic disorder.⁵ In contrast, although Yo-Ab-associated symptoms are more restricted to cerebellum, the disease has a fast and aggressive course and most patients become bed bound during the first 3 months after diagnosis. This clinical evolution coupled with our finding that 37% of the patients developed PCD when they were on antineoplastic treatments or when the tumor was in remission suggest that treatment of the tumor alone is not enough to stabilize the disease at the time the cerebellar dysfunction is not severe.

Although there is experimental and limited clinical evidence that cytotoxic T lymphocytes may be responsible for the death of Purkinje cells,⁹ conventional immunotherapies are not helpful for PCD, probably because their mechanism of action is too slow compared with the aggressiveness of the immune reaction against the Purkinje cells of the cerebellum in the majority of these patients. A rapid abrogation of this immune attack against the nervous system could in theory be achieved with protocols of autologous stem-cell transplantation. This

therapy is currently under evaluation in several aggressive autoimmune disorders.¹⁰ In selected patients with anti-Yo-associated PCD (those younger than 60 years, with no evidence of tumor, and who are ambulatory) the efficacy of autologous stem-cell transplantation could be considered in the setting of a controlled protocol. In patients with more indolent neurologic symptoms, a less aggressive immunosuppression should be attempted on the basis of experimental evidence supporting an immunopathogenesis for PCD. Although theoretically, immunosuppression could exacerbate tumor growth, we did not find that to be the case, and, as occurred in anti-Hu-associated paraneoplastic encephalomyelitis,⁵ treatment with several immunotherapies was not found to be an adverse prognostic factor for survival.

Acknowledgment

The authors thank all the neurologists who provided clinical information about their patients.

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