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## CSF STUDY IN PARANEOPLASTIC SYNDROMES

**Manuscript type:** brief communication

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## **Abstract**

**Objective:** Paraneoplastic neurological syndromes (PNS) probably result from an immune reaction against antigens shared by the nervous system and tumour cells. To characterize CSF alterations in these syndromes, we studied a large series of paraneoplastic patients.

**Methods:** Using the PNS European database which includes patients diagnosed with PNS in Europe, we reviewed the clinical data of all patients included between 2000 and 2007 for which information on the CSF was available. Patients were studied if they met the following inclusions criteria: a) definite paraneoplastic disease with anti-Hu, anti-Yo, anti-CV2, anti-Ri anti-Ma/Ta and anti-Tr antibodies; b) clinical information available; c) at least 1 CSF study.

**Results:** 295 patients met the inclusion criteria. Abnormal CSF (pleiocytosis and/or high protein level and/or oligoclonal bands) was found in 93% of the patients. Pleiocytosis, but not hyperproteinorachia, was more frequently seen in patients in whom the CSF study was done early in the evolution. In 24 patients, OCB were the only abnormality found in the CSF (10%). Elevated numbers of cells were found in 47% of the patients before the 3<sup>rd</sup> month, vs 28% after the 3<sup>rd</sup> month ( $p < 0.01$ ). This evolution might suggest a sub-acute inflammation phase within the nervous system, followed by a non-inflammatory phase. The inflammation profile was similar in all antibody types, cancers or neurological syndromes of the PNS. Surprisingly, anti-Hu patients with high pleiocytosis at time of diagnostic had a better survival in this study than those without pleiocytosis, (572 days vs 365 days,  $p = 0.05$ )

**Conclusion:** CSF inflammation is a common finding in PNS patient and can be a helpful tool for the diagnosis, especially if this analysis is done within 3 months after neurological onset.

## Introduction

Paraneoplastic neurological syndromes (PNS) are characterized by inflammation of the nervous system, indolent tumor growth and an immune reaction against antigens shared by the nervous system and the tumor cells (Dalmau and Posner, 1999). Antibodies (Abs) against these antigens are sometimes identified in the patients' sera and are strongly associated with paraneoplastic syndromes (Dalmau et al, 1992, Luque et al, 1991, Rosenfeld et al, 2001, Peltola et al, 1998, Peterson et al, 1992, Graus et al, 2001, Honnorat et al, 1996).

Abnormalities of the cerebro-spinal fluid (CSF) have been reported in paraneoplastic patients, and probably reflect the inflammatory nature of these diseases. However, the frequency, the relationship with clinical features and the evolution over time of the CSF abnormalities have never been thoroughly described. We therefore studied CSF features in a large series of paraneoplastic patients with anti-Hu, anti-Yo, anti-CV2, anti-Ri anti-Ma/Ta and anti-Tr antibodies.

## Patients and Methods

The PNS European database includes patients diagnosed with PNS in Europe after 2000. The database records information on the neurological symptoms, tumour diagnosis, treatments and outcome.

We reviewed the clinical data of all patients included in this PNS European database before November 2007, for whom CSF information was available. Patients were studied if they met the following inclusion criteria: a) definite paraneoplastic disease with anti-Hu, anti-Yo, anti-CV2, anti-Ri anti-Ma/Ta or anti-Tr antibodies in the serum; b) clinical information available (type of neurological syndrome, date of neurological onset) c) at least 1 CSF study with records of cell count (white cells/mm<sup>3</sup>: normal  $\leq 5$  wc/mm<sup>3</sup>) and protein content (mg/dl: normal between 20 and 50 mg/dl). When available, presence of oligoclonal bands (OCB) in the CSF was collected, although the paired serum OCB status was usually not stated in the medical records. In patients who had several lumbar punctures, only the first CSF study was considered for the global analysis.

Neurological syndromes were classified as limbic encephalitis, encephalomyelitis, cerebellar degeneration, brainstem encephalitis (including opsoclonus) and peripheral nerve disorders (sensory neuronopathy, polyneuropathy, chronic inflammatory demyelinating polyneuropathy, Guillain Barre syndrome, dysautonomia, and motor neuron disease), following the diagnostic criteria of the PNS Euronetwork (Graus for the PNS Euronetwork, 2004). Tumors were classified as small cell lung carcinoma (SCLC), non small cell lung carcinoma (NSCLC), breast cancer, testicular cancer, gynecological (ovary and uterus) cancer, Hodgkin diseases, and others.

The categorical variables were expressed by proportions and the continuous ones were described with mean, median and inter-quartile range. The Pearson chi-square test was used to compare qualitative variables while the Mann-Whitney-Wilcoxon rank test was used for quantitative ones. Survival analysis was performed through Kaplan–Meier method to compare patients with normal vs. abnormal cell count. Differences in survival time from syndrome onset were evaluated through the Log-Rank test. All tests were two-tailed, with 0.05 as the level of significance. Data were analyzed using SAS software (version 9.02, SAS System, Cary, NC).

## Results

Out of 829 patients registered in the database in November 2007, 295 patients met the inclusion criteria. The patients' characteristics are summarized in table 1 and 2. The most frequent antibody was anti-Hu (58%) followed by anti-Yo (20%), anti-CV2 (8%), anti-Ma/Ta (6%), anti-Ri (5%) and anti-Tr (3%). Among the 170 patients with anti-Hu Abs, 9 had anti-CV2 Abs, 8 had anti-Ri Abs, 5 also had anti-amphiphysine Abs, one had anti-VGCC Abs, two had anti-Yo Abs, one had anti-Tr Abs and 5 had other or atypical Abs. Most patients with anti-Hu Abs had peripheral nerve disorders and SCLC (44% and 64%, respectively) (Appendix 1 and 2). Cerebellar degeneration was the main clinical syndrome in anti-Yo (92%) and anti-Tr (89%) patients. PEM was almost always associated with anti-Hu antibodies (91%) and very often with SCLC tumours (72%). The frequency of brainstem encephalitis was higher in anti-Ri group (60%) and limbic encephalitis in anti-Ma/Ta group (58%). No tumour was found in 41 patients (14 %).

**Table 1**

	Anti-Hu	Anti-Yo	Anti-CV2	Anti-Ma/Ta	Anti-Ri	Anti-Tr
<b>N</b>	170	59	23	19	15	9
<b>F/M</b>	67/103	57/2	7/16	4/15	12/3	2/7
<b>Mean age (Sd : Q1-Q3)</b>	66 (58-72)	65 (59-72)	68 (61-78)	55 (42-69)	66 (52-75)	58 (50-71)
<b>Neurological syndrome</b>						
-peripheral nerve disorders	74	1	9	0	0	0
-limbic encephalitis	14	0	1	11	3	1
-Brainstem encephalitis	16	1	0	4	9	0
-Cerebellar degeneration	12	54	3	3	3	8
-PEM	29	1	2	0	0	0
-Other	25	2	8	1	0	0
<b>Cancer</b>						
-SCLC	109	0	12	0	0	0
-NSCLC	11	1	2	1	1	0
-Testicular	0	0	0	6	1	0
-Breast	4	11	1	2	8	0
-Gynaecological	0	32	0	0	0	0
-Hodgkin	0	0	0	0	0	6
-No tumour	23	5	4	6	2	1
-Others	23	10	4	4	3	2

Cells were studied in 290 patients and found to be superior to 5 wc/mm<sup>3</sup> in 112 patients (39%) (median cell level: 3 wc/mm<sup>3</sup>). Proteins were studied in 281 patients and found to be higher than 50 mg/dl in 187 patients (67 %) (median protein level: 68 mg/dl). Presence of oligoclonal bands (OCB) in the CSF was studied in 135 patients and found positive in 85 patients (63%). In 24 patients, OCB were

the only abnormality found in the CSF (10%). In patients in whom pleiocytosis, proteinorachia and oligoclonal bands were all studied, completely normal CSF was found in only 7% of patients (18/260).

**Table 2**

	Anti-Hu	Anti-Yo	Anti-CV2	Anti-Ma/Ta	Anti-Ri	Anti-Tr
<b>N</b>	170	59	23	19	15	9
Abnormal (%)	93% (140/151)	96% (51/53)	95% (20/21)	87% (13/15)	100% (13/13)	71% (5/7)
Median delay after clinical onset (Q1-Q3)	79 days (27-166)	76 days (31-184)	66 days (22-147)	106 days (30-243)	84 days (16-125)	44 (29-109)
Median number of cells (Q1-Q3)	3 (1-8)	4 (1-22)	5 (1-12)	3 (1-20)	5 (1-15)	7 (3-10)
Median number of protein (Q1-Q3)	78 (49-135)	54 (36-80)	75 (57-100)	53 (39-70)	55 (39-415)	41 (25-72)
Positive oligoclonal bands	43/73	25/33	6/8	5/10	6/8	0/3

To describe the CSF abnormalities over time, we plotted the cell and the protein values on the y-axis and the delay from neurological onset to the CSF study on the x-axis, in patients who did not receive any treatment before the CSF study (n=206) (Figure 1). The CSF study was done within the first 3 months after neurological onset in 162 patients. Elevated numbers of white cells were found in 47% of these patients, versus 28% after the 3<sup>rd</sup> month (Pearson chi-square test, p<0.01). The median level was 5 cells/mm<sup>3</sup> before the 3<sup>rd</sup> month and 2 cells/mm<sup>3</sup> after (Mann-Whitney-Wilcoxon test, p<0.01). Hyperproteinorachia was observed in 71% of the patients (median 73 mg/dl) before the 3<sup>rd</sup> month and in 61% (median 59 mg/dl) after the 3<sup>rd</sup> month (Mann-Whitney-Wilcoxon test, p<0.01). OCB were found in 63% (42 out of 67) of the patients and the same after the 3<sup>rd</sup> month (43 out of 68). Within 3 months from neurological onset, in patients in whom pleiocytosis, proteinorachia and oligoclonal bands were all studied, completely normal CSF was found in only in 3% of the patients (11.9% of the patients of completely normal CSF after 3 months from neurological onset).

To further study the possible decrease over time of pleiocytosis, we focused on the few patients who had repeated CSF studies without any treatment between two CSF tests. There were 15 patients with both CSF studies done before day 90, and 17 patients in whom the second CSF study was done after day 90 (appendix 5). The median time point of the first CSF study was 18 and 87 days respectively for both groups. The pleiocytosis appeared or increased in 7 patients out of 15 when both CSF studies were made before the first 3 months, but only in 1 patient out of 17 when the second lumbar puncture was done after the first 3 months (p=0.009). Similarly, when the analysis was limited to the 23 patients showing at least one abnormal CSF, the decrease in pleiocytosis was more frequent when the second CSF study was done after the first 3 months (p=0.03)

To investigate whether oncological or immunological treatments could impact CSF abnormalities, we looked at the 12 patients who had two CSF studies and were treated in between. The difference between cells and proteins before and after treatment was not statistically significant (median cell level: 9 cells/mm<sup>3</sup> before treatment and 4.5 cells/mm<sup>3</sup> after treatment; median protein level: 86 mg/dl before treatment and 86 mg/dl after treatment).

We then focused on the pattern of CSF abnormalities within 3 months, depending upon the antibody or the cancer types. Surprisingly, no significant difference was seen in the protein levels or in the cell reaction among the various antibodies or cancers, although there was a trend for higher protein levels in patients with anti-Hu and anti-CV2 Abs or lung cancer (SCLC and NSLC). See appendix 3 and 4.

We compared the CSF in patients with central or peripheral (190 vs 103 patients) PNS. When the CSF study was done within 3 months after neurological onset (central –n=115-, peripheral – n=45-) pleiocytosis was more pronounced in central PNS than in peripheral PNS (median: 6 vs 3 cells/mm<sup>3</sup>; Mann-Whitney-Wilcoxon test, p=0.14), while proteinorachia showed the opposite figure (median 68 vs 100 mg/dl; Mann-Whitney-Wilcoxon test, p<0.01). The percentage of positive OCB was the same between central and peripheral PNS (35% vs 41%).

We then wondered whether pleiocytosis and protein at time of diagnosis could have a prognostic value in paraneoplastic patients (figure 2). To address this issue, we selected the anti-Hu patients (the other antibodies were not studied because of the low number of patients) who had a CSF study within 3 months from clinical onset (n=92). Patients were divided into two groups; those with a normal cell count in the CSF (n=56) and those with more than 5 cells/mm<sup>3</sup> (n=35). The clinical characteristics that are known to be of prognostic value were similar in both groups. The median Rankin score was 3 at time of neurological onset in both groups. PEM was as frequent in both groups (23% vs. 18%, respectively). Peripheral disorders were slightly lower in patients with pleiocytosis (37% vs. 47% respectively). The median age was the same in both groups (65y vs. 66y). Surprisingly, the group with CSF pleiocytosis showed a better median survival than the group without (572 days vs 365 days; Log-Rank test, p=0.05). Protein levels were not correlated with survival (data not shown).



## Discussion

Paraneoplastic Neurological Syndromes (PNS) are believed to be immune mediated. Inflammation of the CSF is a common finding in that setting, but no dedicated study has been published so far. Here we report the largest CSF study in PNS, showing that abnormal CSF is almost always seen in these patients, especially early in the course of the disease.

Abnormal CSF was recorded in most patients (93%). This figure fits with the limited CSF data published in series of paraneoplastic patients with anti-Hu (Dalmau et al, 1992), anti-Yo (Peterson et al, 1992), anti CV2/CRMP5 (Yu et al, 2001), anti-Ta (Dalmau et al, 2004), anti-Tr (Bernal and al, 2003) or anti-Ri antibodies (Pittock and al, 2003), with a frequency of abnormal CSF ranging from 59 and 86% of patients. The presence of OCB in CSF has been reported in approximately 75% of the patients with paraneoplastic diseases (Peterson et al, 1992; Dalmau et al, 1992; Gultekin et al, 2000; Dalmau et al, 2004), and their specificity against the paraneoplastic antigens have been documented (Rauer et Kaiser, 2000; Stich et Rauer, 2007). However, the unclear status of the serum OCB in the medical records of our CSF study represents a methodological limitation, as intrathecal antibody synthesis cannot be stated. Indeed, positive OCB in the serum, related or not to the paraneoplastic disease, could have passively diffused into the CSF (Deisenhammer et al, 2006).

In our series, pleiocytosis was more frequent in patients in whom the CSF study was done early after neurological onset. The median level of cells was 5 white cells/mm<sup>3</sup> before the 3<sup>rd</sup> month and 2 white cells/mm<sup>3</sup> after. The incidence for proteinorachia also decreased but stayed at abnormal levels (median level 73 mg/dl before the 3<sup>rd</sup> month and 59 mg/dl after). This evolution fits with the acute or sub-acute course of the disease, with early neuronal loss during the first months, followed by a non-inflammatory phase when all neurons have disappeared. However, a potential bias in the decrease over time of pleiocytosis can be advocated. One can imagine that patients with highly inflammatory diseases have a CSF study early in the evolution, while those with a poorly active or atypical disease, have a CSF study later on. Serial CSF analysis in a prospective study should easily exclude this hypothesis. In our study, when several CSF studies were available, increase in pleiocytosis was more frequent in patients in whom both CSF studies were done within the first 3 months, compared to patients with a second CSF done after 3 months. However, the median time point of the first CSF study was different between both groups and might have introduced a bias.

The inflammatory CSF, especially during the acute stage, is in line with radiological and pathological studies. Hypermetabolism in FDG-Pet scan and increased perfusion on SPECT have been described in paraneoplastic limbic encephalitis and paraneoplastic cerebellar degeneration (Choi et al, 2006), attributed by the authors to inflammatory changes. Neuropathological studies of PCD performed within 1 year after the onset of neurological symptoms generally show severe loss of Purkinje cells in combination with various degrees of inflammatory, mainly lymphocytic, infiltrates, while studies performed more than 1 year after the onset showed absence of inflammatory infiltrates (Giometto et al, 1997). This early inflammation suggests that an early treatment might be beneficial for the clinical outcome.

Several unexpected results were found in our study. The CSF profile was quite similar in all antibody types, cancers or neurological features of the PNS; although there was a trend for higher protein levels in patients with anti-Hu abs, SCLC and peripheral disorders, this did not reach statistical significance. In addition, the CSF features were similar regardless of whether the patients were treated (cancer or immunomodulatory treatments) before CSF study or not. This probably reflects the poor efficacy of the currently available treatments.

However, the most intriguing finding of our study is the shorter survival of anti-Hu patients with low CSF inflammation when compared to patients with pleiocytosis, although both groups showed similar clinical characteristics, including Rankin scores. This cannot be explained by imbalanced delays from onset to CSF study between both groups, since we selected only the patients who had a lumbar puncture within 3 months after neurological onset. Obviously, due to the limited number of patients, this result needs to be confirmed in a large prospective study. This better survival could be related to a slower tumour growth and/or better tumour response in patients who developed a strong immune response. This could also be related to greater sensitivity to immunological treatment in patients with a high inflammatory response, as reported in neurosarcoïdosis (Hoitsma E et al, 2004) or even in multiple sclerosis (Polman for AFFIRM study, 2006 and Jacobs for CHAMPS study, 2000).

In conclusion, CSF inflammation is very common in PNS patient and could be a helpful diagnostic tool, especially if this analysis is done within 3 months after neurological onset. Preliminary data show that patients with pleiocytosis at the time of diagnosis might have a better survival, but this finding should be confirmed in a larger, prospective study.

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## Legends to tables and figures

**Table 1:** Patient characteristics (F/M: female/male, PEM: paraneoplastic encephalomyelitis, SCLC: small cell lung cancer, NSCLC: no small cell lung cancer, CSF: cerebrospinal fluid).

**Table 2:** Q1 is the first quartile (id 25% of patients are under Q1). Q3 is the third quartile (id 75% of patients are under Q3).

**Figure 1:** evolution over time after neurological onset of cells and proteins in cerebrospinal fluids.

**Figure 2:** survival of patients with anti-Hu antibodies who had a CSF study within 90 days after neurological onset. Patients were divided into 2 groups; those with a normal cell count in the CSF (black; n=56) and those with more than 5 white cells/mm<sup>3</sup> (grey; n=35). The group with CSF inflammation showed a better median survival than the group without (572 days vs 365 days, p= 0,05).

**Appendix 5:** Cell numbers in the CSF (cells/mm<sup>3</sup>) in the patients who had repeated CSF studies without any treatment between two CSF tests.

	both CSF analysis before day 90 (n=15)	second CSF analysis after day 90 (n=17)
median cell number at first CSF study	9	7
median cell number at second CSF study	20	2
normal cell numbers in both CSF	3 patients	6 patients
decrease in pleiocytosis between both CSF	5 patients	10 patients
increase in pleiocytosis between both CSF	7 patients	1 patient

Figure 1

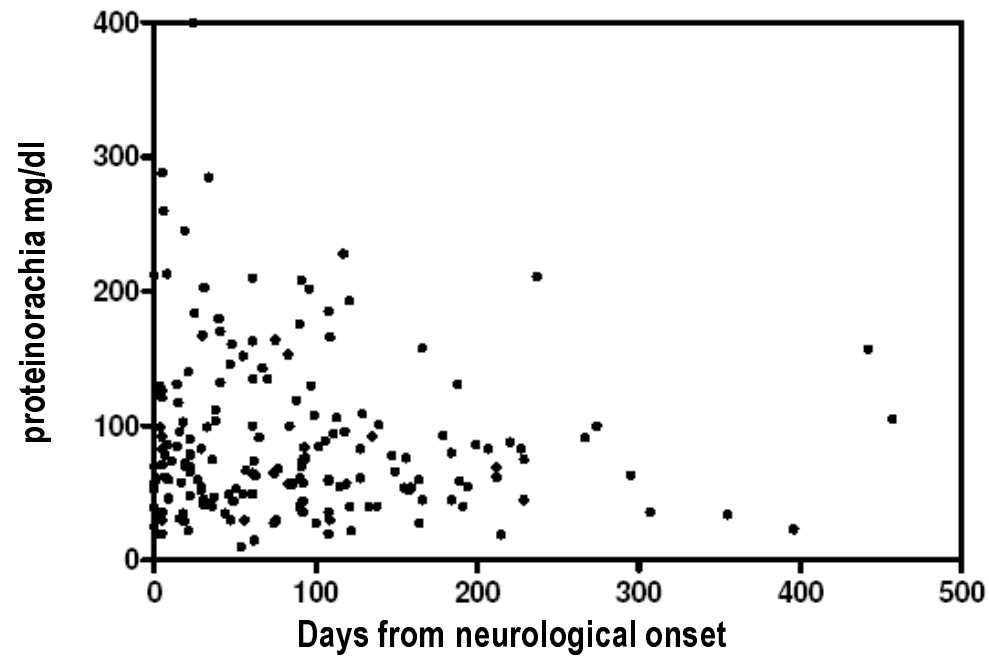
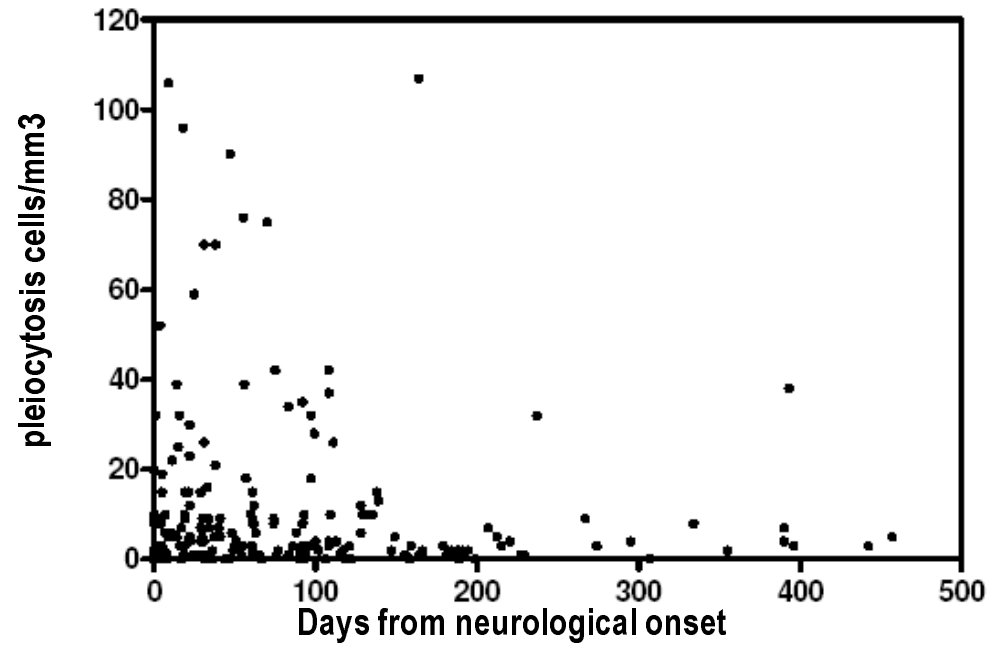
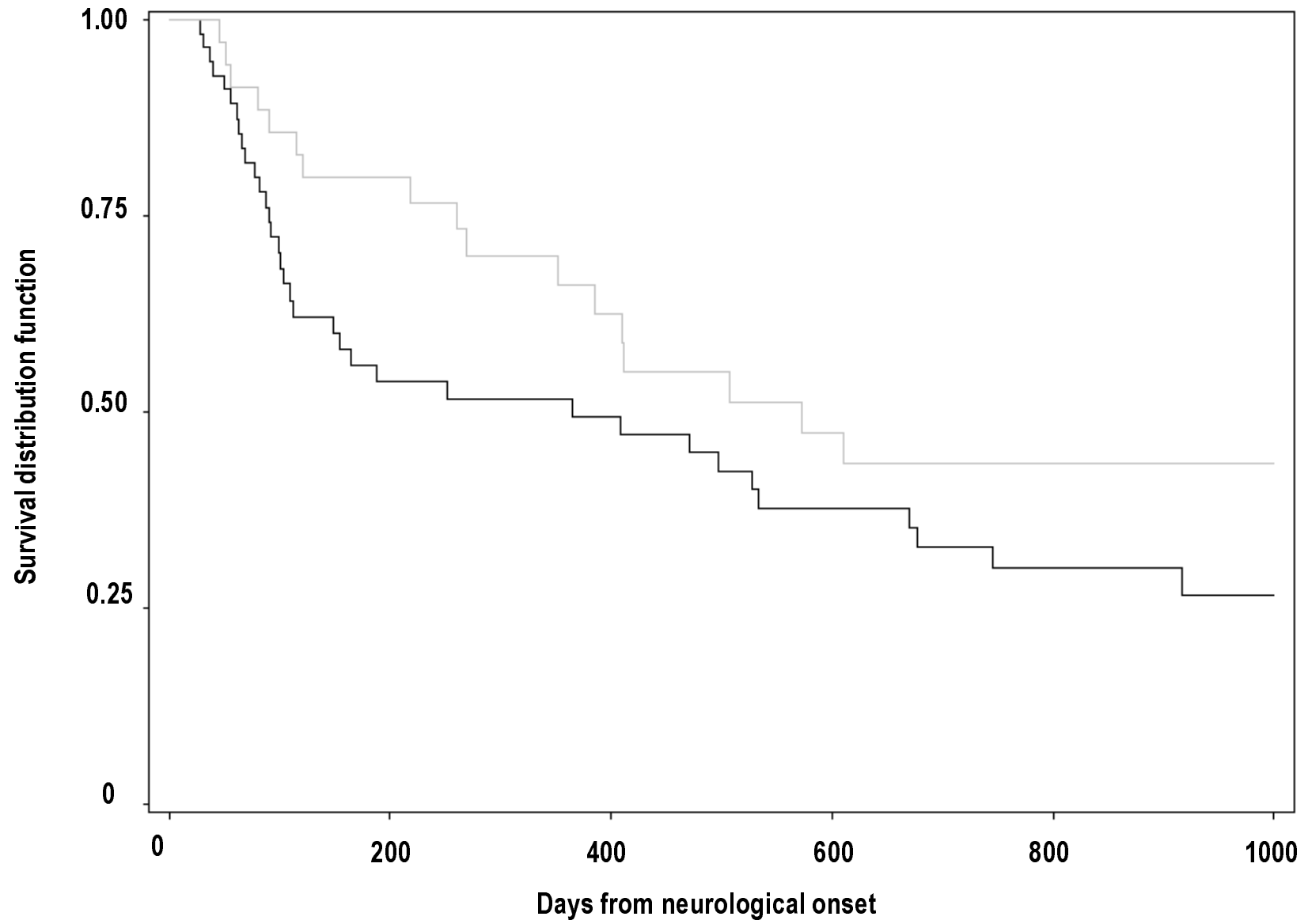
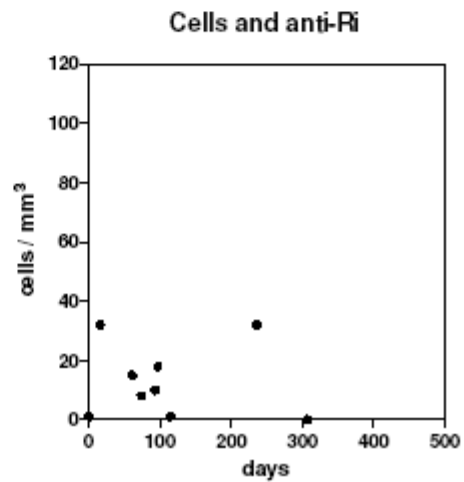
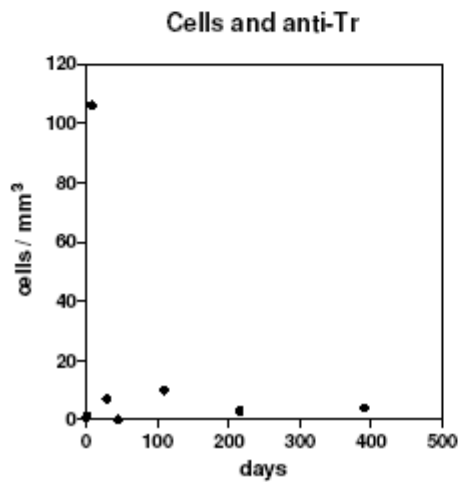
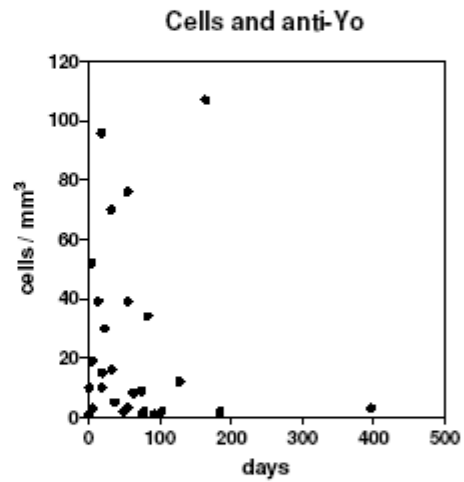
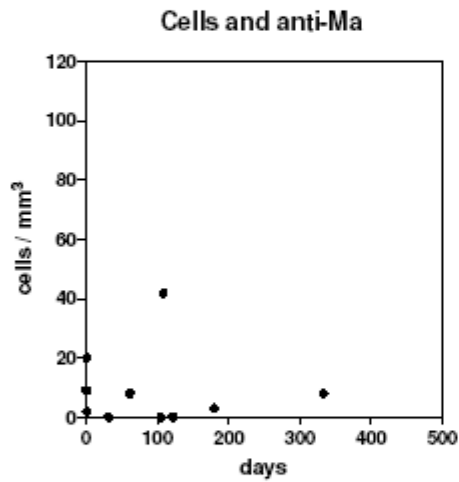
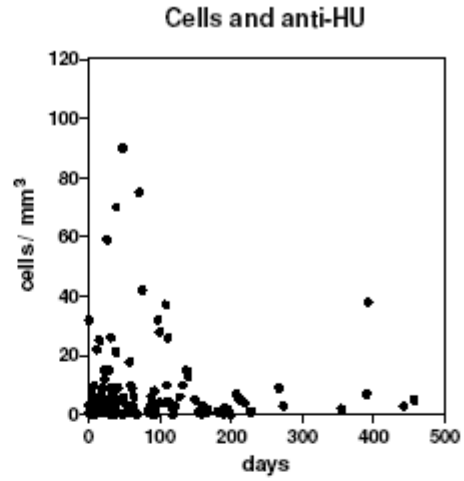
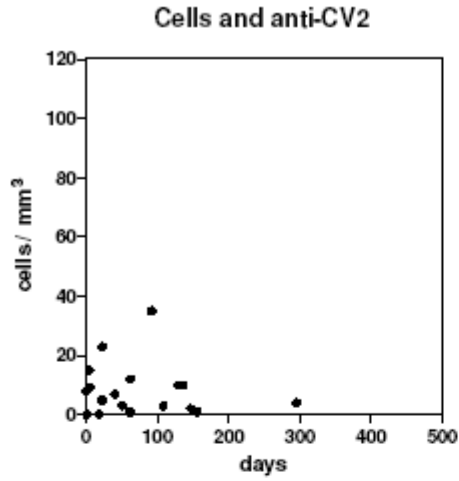


Figure 2

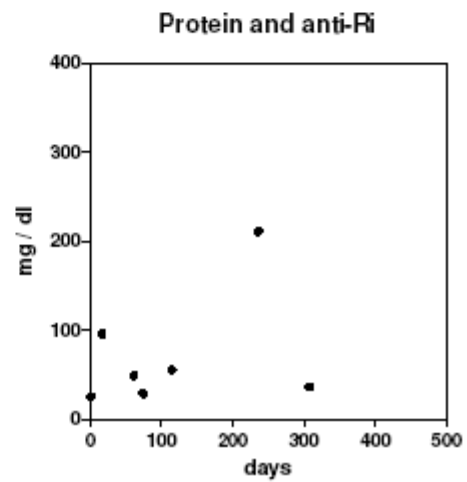
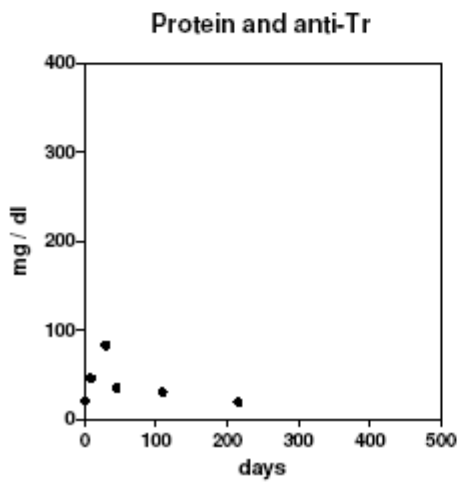
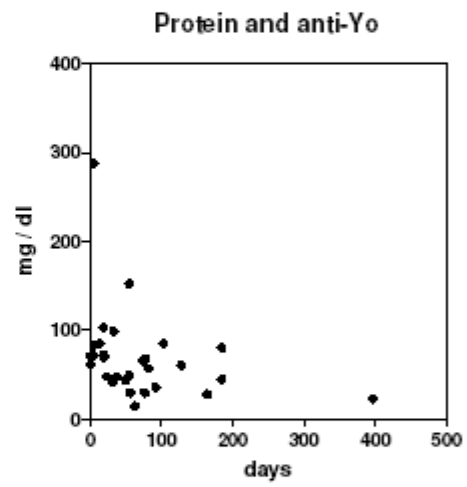
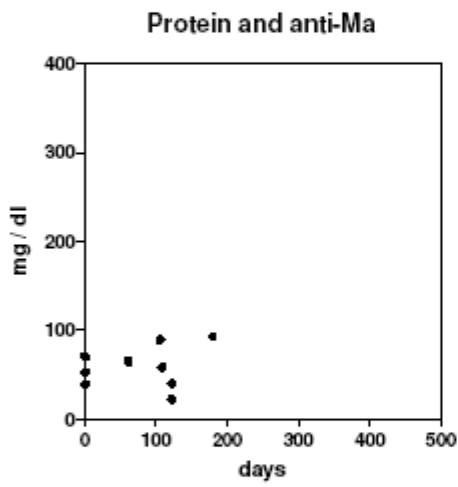
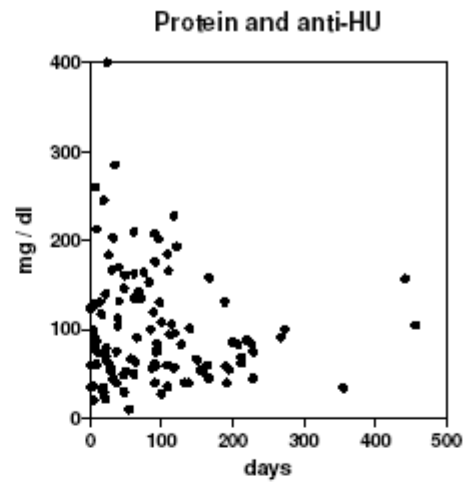
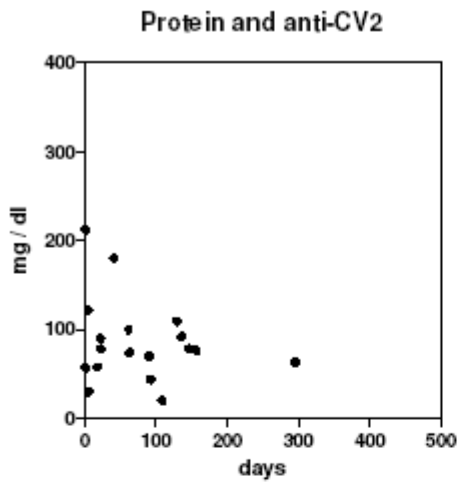




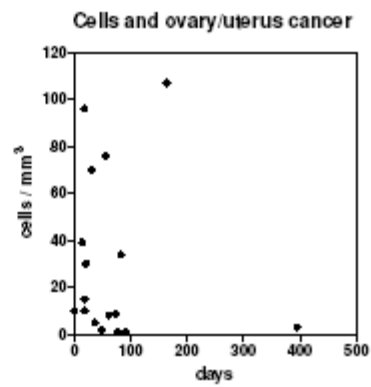
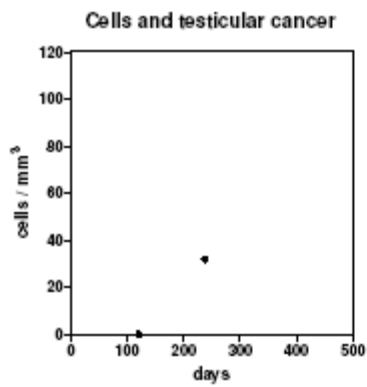
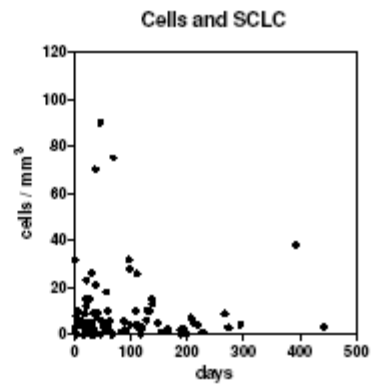
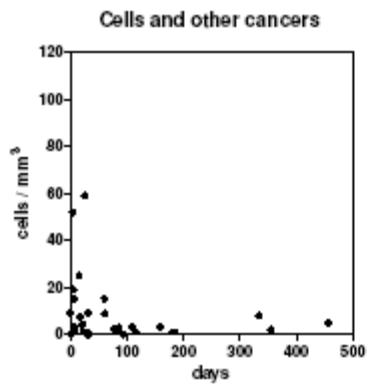
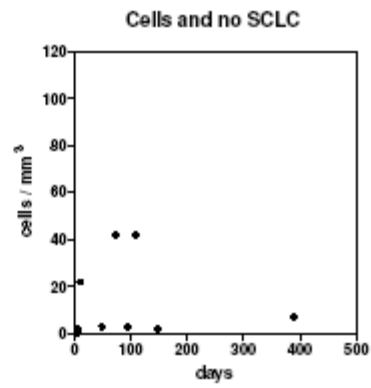
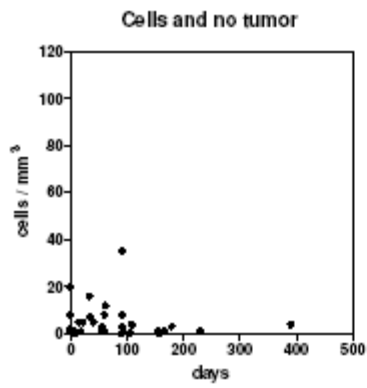
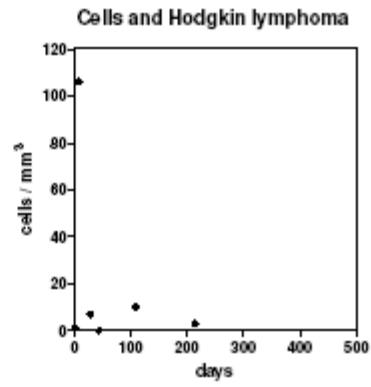
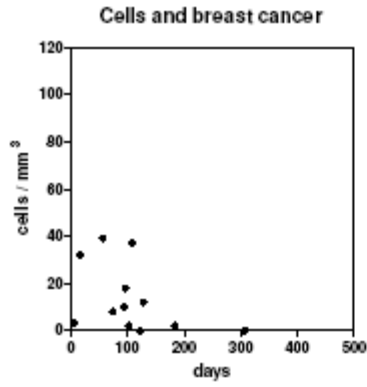
# Appendix 1, cells



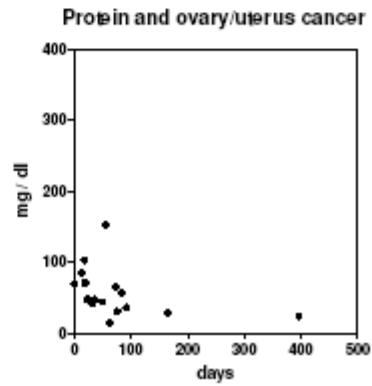
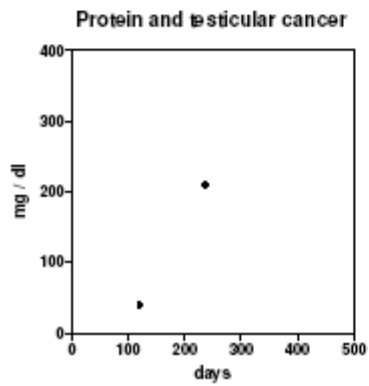
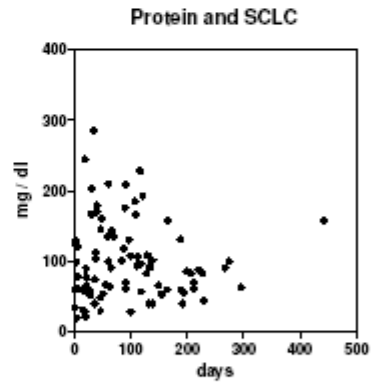
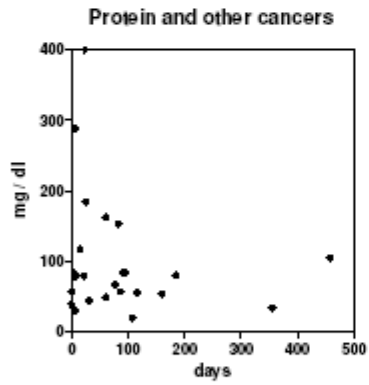
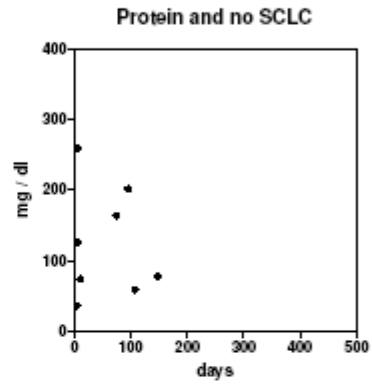
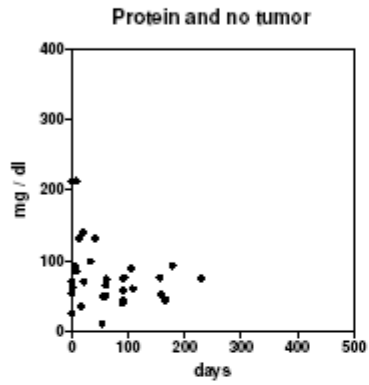
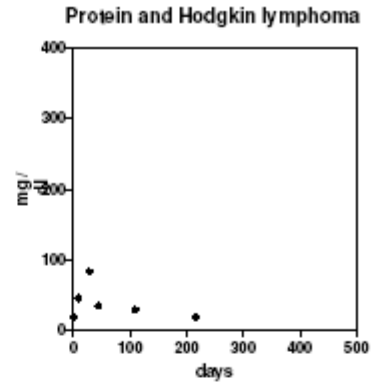
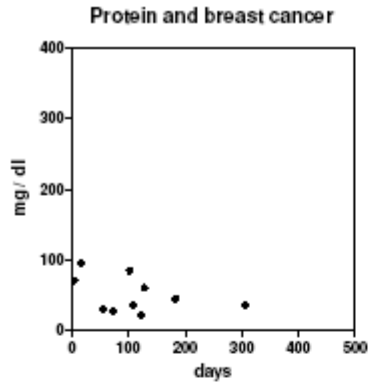
# Appendix 1, protein



# Appendix 2, cells



# Appendix 2, protein



## Appendix 3 and 4

	<b>Anti-Hu</b>	<b>Anti-Yo</b>	<b>Anti-CV2</b>	<b>Anti-Ma/Ta</b>	<b>Anti-Ri</b>	<b>Anti-Tr</b>
Cells $\geq$ 5 wc/mm <sup>3</sup>	38%	57%	50%	75%	57%	67%
Protein > 50 mg/dl	80%	54%	82%	71%	50%	50%
Positive oligoclonal bands	20/34	15/19	2/4	2/4	3/4	0/2

	<b>SCLC</b>	<b>NSCLC</b>	<b>Testicular Cancer</b>	<b>Breast Cancer</b>	<b>Gynecological Cancer</b>	<b>Hodgkin Lymphoma</b>
Cells $\geq$ 5 wc/mm <sup>3</sup>	40%	29%	100% (2/2)	43%	65%	50%
Protein > 50 mg/dl	83%	83%	100% (2/2)	44%	48%	25%
Positive oligoclonal bands	16/28	1/3	1/1	3/6	10/11	0/2