Table 1 Clinical features of patients with transient global amnesia after gastroscopy

Age (years), sex	Vascular risk	Episode duration (h)	Previous gastroscopy (times)	Premedication	Pharyngeal lidocaine spray	Experience of endoscopist (years)
58, Female	Hypertension	7.5	1	None	Yes	35
59, Female	None	Approximately 15	2	Scopolamine	Yes	14
65, Female	Hyperlipidaemia	8	12	Scopolamine	Yes	35

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Hu-antibody-positive patients with or without cancer have similar clinical profiles

Hu-antibodies (Hu-abs) are markers of paraneoplastic neurological syndrome (PNS), almost always associated with small-cell lung carcinoma. A few patients with PNS who are Hu-ab positive, however, never develop cancer after long-term follow-up.[1] If there were clinical differences, they could help identify those Hu-ab-positive patients who would not need serial screening for cancer. In this study, we analysed the clinical profile of Hu-ab-positive patients without cancer after a follow-up of more than 3 years and compared the findings with those in Hu-ab-positive patients with a tumour.

Methods

Of a total of 608 patients from our databases, we retrospectively identified 68 patients with PNS who were positive for Hu-abs, and had a follow-up of at least 3 years from the onset of the neurological syndrome. Patients were divided into two groups, according to the presence or absence of cancer during the follow-up. All patients without cancer underwent at least a CT of the chest. All of them had serial clinical and radiological (CT or chest *x* ray) examinations during the follow-up.

We analysed the following variables: age, sex, smoking habit, type of PNS, time to diagnosis of Hu-ab syndrome and Rankin score at diagnosis and at last visit. Data were analysed with SPSS V.10.0. The ethical committee of the hospital clinic approved the study.

Results

We identified 68 Hu-ab-positive patients (3% of the whole series) with a clinical follow-up of more than 3 years, 49 with and 19 without cancer. Table 1 summarises the clinical features of these patients. In the group without tumour, the youngest patient was a 28-year-old woman with polyradiculoneuropathy and systemic lupus erythematosus (SLE).[2] The remaining patients had no other autoimmune diseases. A detailed report on the presence of autoimmune disorders, however, was not routinely registered in the databases. A 61-year-old man, with cerebellar ataxia and opsoclonus, had a severe premalignant bronchial dysplasia at initial bronchoscopy, but the mucosa was normal at three subsequent bronchoscopies over the following months. Six patients without cancer died during the follow-up: four from PNS, one from heart disease and one of unknown cause. Postmortem examination was not performed.

In the group of 49 patients with cancer, the tumour was diagnosed before the third year in 46 (94%) patients. The other three patients were diagnosed with metastatic small-cell lung carcinoma at 40, 41 and 72 months, respectively, after the onset of PNS.

We found no differences between the groups in any of the variables analysed, with the exception of the average duration of follow-up. This was significantly longer in the group without tumour (84 *v* 68 months, $p = 0.048$). In this group, the follow-up was longer than 72 months in 11 (58%) patients. Because one patient had cancer diagnosed 72 months after the onset of PNS, we compared the clinical variables of those 11 patients without cancer with those of patients with cancer after more than 72 months of follow-up. We found no differences, except for an increase in the time between the onset of PNS and detection of Hu-abs (table 1).

Discussion

In our study, 3% of all Hu-ab-positive patients with PNS did not develop a tumour during prolonged follow-up. We found no clinical features that distinguished the few Hu-ab-positive patients who did not develop cancer from those who did. Our use of the 3-year cut-off was based on previous studies on PNS in which almost all tumours were

Table 1 Clinical characteristics of patients with and without tumour with a follow-up of more than 36 and 72 months

	Tumour*	No tumour >36 months	p Value	No tumour >72 months	p Value
Number of patients	49	19		11	
Age of onset, years (range)†	58 (37–74)	54 (28–81)	0.24	52 (28–68)	0.121
Male	36 (73.5)	10 (52.6)	0.19	5 (45.5)	0.086
Smoker‡	32 (97.0)	15 (83.3)	0.12	9 (90.0)	0.415
Rankin score at diagnosis					
0–3	37 (75.5)	15 (78.9)	1.0	9 (81.8)	1.0
4–5	12 (24.5)	4 (21.1)		2 (18.2)	
Rankin score at follow-up§					
0–3	25 (64.1)	13 (72.2)	0.80	8 (80.0)	0.45
4–5	14 (35.9)	5 (27.8)		2 (20.0)	
Predominant syndrome					
Involvement of CNS¶	6 (12.2)	4 (21.0)	0.26	2 (18.2)	0.60
No involvement of CNS**	43 (87.8)	15 (79.0)		9 (81.8)	
Time between onset of PNS and detection Hu, months (range)	12.8 (0–60)	19.8 (3–65)	0.08	24 (5–65)	0.04

CNS, central nervous system; PNS, paraneoplastic neurological syndrome; SCLC, small-cell lung carcinoma.
Values in parentheses are percentages, unless otherwise stated.
*SCLC, 36; non-SCLC, 6; breast cancer, 3; bladder cancer, 1; ethmoidal epithelioma, 1; thymoma, 1; germ cell tumour, 1.
†Patients under 40 years (1 with tumour, 4 without tumour).
‡Status unknown in 17 patients (16 with tumour, 1 without tumour).
§Rankin score unknown in 11 patients (10 with tumour; 1 without tumour).
¶Tumour group: cerebellar degeneration, 3; limbic encephalitis, 2; encephalomyelitis, 1. Non-tumour group: cerebellar degeneration, 3; brain stem encephalitis, 1.
**Tumour group: sensory neuronopathy, 41; dysautonomia, 2. Non-tumour group: sensory neuronopathy, 11; sensorimotor neuropathy, 3; dysautonomia, 1.

diagnosed within this period.[1] Our study confirmed the validity of this choice as only 6% of tumours developed between 3 and 6 years from the onset of PNS. When we analysed the subgroup of 11 Hu-ab-positive patients without cancer with a follow-up of more than 6 years, we found no clinical feature predicting this course.

The onset of PNS in patients over 40 years of age and with a history of smoking are both considered to be clinical clues for underlying cancer. Our study, however, shows that these variables are imperfect predictors. More than 80% of our Hu-ab-positive patients without cancer were smokers. Although three of four Hu-ab-positive patients under 40 did not develop cancer, one of them did. These data emphasise that young age may help predict the absence of cancer, but it cannot be taken as a definite predictor.

The youngest patient in our series of patients without cancer was 28 years old and had an associated SLE.[2] The presence of a systemic autoimmune disorder in a patient with Hu-abs, however, should be evaluated with caution. In a previous study, 2 of 173 patients with primary Sjögren's syndrome or SLE had Hu-abs and one of them developed small-cell lung carcinoma.[3] In patients with the Lambert–Eaton myasthenic syndrome, the incidence of autoimmune diseases in patients with cancer was 11%.[4] Thus, the presence of a systemic autoimmune disorder in a patient with Hu-abs does not rule out the possibility of a concomitant neoplasm.

In about 70% of our patients without cancer, the disability caused by PNS was mild or moderate (Rankin score <4). This proportion is considerably higher than that reported in previous studies on Hu-abs-positive patients and probably represents a selection bias.[1] Patients without cancer and with severe PNS are more likely to die from PNS within 3 years.

Anecdotal case reports suggest that the Hu-mediated immune response may destroy an underlying cancer.[5] If this hypothesis is correct, one would predict that the cytotoxic immune response would be more effective when the tumour is at the microscopic stage and therefore undetectable by even the most sensitive imaging techniques. The absence of distinguishing clinical features between Hu-ab-positive patients without cancer and those who develop cancer supports the possibility that these patients developed an effective Hu—probably a T cell-mediated—immune response that eliminated the tumour at an early stage of its development.

In conclusion, our study confirms that all patients with Hu-abs require regular examinations for underlying malignancy whatever their clinical features, including age, smoking habit and history of systemic autoimmune disease.

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Niemann–Pick type C disease in a 68-year-old patient

Niemann–Pick disease type C (NPC) is an autosomal recessive neurovisceral lipid storage disease resulting from mutations of either the NPC1 (95% of families) or the NPC2 gene, showing a wide spectrum of clinical phenotypes and a highly variable age at diagnosis.[1 2]

We report NPC1 in the oldest patient affected with the disease so far. This 68-year-old woman presented with a 15-year history of depression and fluctuating mood, and was treated several times in psychiatric departments during the previous years. At the age of 54 she was unable to work further. In the past 4 years she had developed a fluctuating, progressive dementia with reduced impulse, affective instability, dysphagia, cramped hands and dyskinesia. A percutaneous endoscopic gastrostomy was initiated owing to the loss of considerable body weight in the previous months. Initial examination, 4 years ago, showed blepharospasm, a vertical gaze palsy and choreiform oral-buccal movements in the patient. She was bedridden and was not able to communicate, was only intermittently groaning and followed simple requests inconstantly. Her hands were held in a dystonic, flectional position and her upper extremities were moved stereotypically. A positive bilateral Babinski sign was found. Cerebral MRI showed a mild cerebellar atrophy and some isolated periventricular signal intensities in the T2/TIRM. Protein was slightly enhanced (73.7 mg/dl) in CSF, without pleocytosis. Initial electroencephalography showed only a mild slowing. CT of the abdomen showed a mild splenomegaly (14 cm), which was unknown before, and a hepatic steatosis.

Owing to the combination of a slowly progredient neurodegenerative disorder with splenomegaly and vertical gaze palsy, NPC was suspected and confirmed in skin fibroblasts, where filipin staining showed a clear-cut pattern of the variant biochemical subtype.[1]

The NPC1 gene, mapped to chromosome 18q11–q12, spans 56 kb and contains 25 exons. It encodes a 1278-amino-acid integral membrane protein with 13 transmembrane domains.[1 2] Molecular genetic analysis showed a new frameshift mutation of the NPC1 gene, K1206fs, on one allele in our patient. By cDNA sequencing, the second allele remained so far unidentified, a not uncommon situation for patients with NPC1.[1] Neuroimaging of fluorodeoxyglucose (FDG)-PET labelled with fluorine-18 showed remarkable hypometabolism bilateral in thalamic and parietooccipital cortical regions (fig 1), in good agreement with the recent observation that diminished thalamic metabolism is a shared feature on FDG-PET in patients with NPC.[3]

After discontinuation of drug treatment for neuroleptic and Parkinson's disease, the cognitive functions of the patient improved without relevant drugs. Interestingly, during a period of 2 weeks, the patient communicated only in English, a language spoken temporarily during early primary school. Finally, she was able to eat and to communicate in a simplified fashion. At present, 4 years later, the patient lives in a nursing home and still displays fluctuating daily abilities.

Conclusion

NPC represents an autosomal recessive disorder with a major biochemical, molecular and clinical variability. We report on the oldest patient with NPC, which highlights this important, although rare, diagnosis of which neurologists and psychiatrists need to be aware and which, hopefully, might be treated in the near future. Ongoing research suggests that substrate reduction treatment may be able to halt or slow progression of the disease, particularly in milder cases such as the one presented.[4] At present, clinical trials with an inhibitor of glycosphingolipid biosynthesis (miglustat) are under way in patients with NPC.[5]

To enable such treatment, however, the organic cause also has to be identified early in patients with psychiatric presentations. Thus, there is need for a thorough physical and