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Screening for tumours in paraneoplastic syndromes: report of an EFNS Task Force

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Abstract

Background—Paraneoplastic neurological syndromes (PNS) almost invariably predate detection of the malignancy. Screening for tumours is important in PNS as the tumour directly affects prognosis and treatment and should be performed as soon as possible.

Objectives—An overview of the screening of tumours related to classical PNS is given. Small cell lung cancer, thymoma, breast cancer, ovarian carcinoma and teratoma and testicular tumours are described in relation to paraneoplastic limbic encephalitis, subacute sensory neuronopathy, subacute autonomic neuropathy, paraneoplastic cerebellar degeneration, paraneoplastic opsoclonus-myoclonus, Lambert-Eaton myasthenic syndrome (LEMS), myasthenia gravis and paraneoplastic peripheral nerve hyperexcitability.

Methods—Many studies with class IV evidence were available; one study reached level III evidence. No evidence-based recommendations grade A–C were possible, but good practice points were agreed by consensus.

Recommendations—The nature of antibody, and to a lesser extent the clinical syndrome, determines the risk and type of an underlying malignancy. For screening of the thoracic region, a CT-thorax is recommended, which if negative is followed by fluorodeoxyglucose-positron emission tomography (FDG-PET). Breast cancer is screened for by mammography, followed by MRI. For the pelvic region, ultrasound (US) is the investigation of first choice followed by CT. Dermatomyositis patients should have CT-thorax/abdomen, US of the pelvic region and mammography in women, US of testes in men under 50 years and colonoscopy in men and

women over 50. If primary screening is negative, repeat screening after 3–6 months and screen every 6 months up till 4 years. In LEMS, screening for 2 years is sufficient. In syndromes where only a subgroup of patients have a malignancy, tumour markers have additional value to predict a probable malignancy.

Keywords

cancer; neurology; paraneoplastic; screening

Background

Paraneoplastic neurological syndromes (PNS) are rare and occur as a remote effect of tumour, not directly caused by mass lesions, metastases, infections, nutritional factors or anti-tumour treatment. Amongst the tumours associated with PNS, small cell lung cancer (SCLC) is the most frequent one [1]. Other tumours related to PNS are thymoma, ovarian carcinoma and teratoma, breast carcinoma, testicular tumours and Hodgkin's disease. PNS occur in 1–3% of patients with SCLC [2,3], which is far less common than other cancer complications [4]. However, recognition and diagnosis of PNS is important as neurological symptoms almost invariably predate direct symptoms of the primary tumour [5–8], and treatment at earlier stage provides better chance of good outcome. Proper treatment is also important as most paraneoplastic syndromes cause severe disabilities.

Criteria for diagnosis and management of PNS have been published by the PNS Euronetwork [9], in a recent review by Dalmau [10] and by the EFNS Task Force guideline of 2006 [11]. This paper outlines screening recommendations for PNS.

Methods

The Task Force decided to focus on screening of tumours in classical PNS [9]: Lambert-Eaton myasthenic syndrome (LEMS), paraneoplastic limbic encephalitis (PLE), subacute sensory neuronopathy (SSN), subacute autonomic neuropathy (SAN), paraneoplastic cerebellar degeneration (PCD), paraneoplastic opsoclonus-myoclonus (POM), paraneoplastic peripheral nerve hyperexcitability (PPNH), myasthenia gravis (MG) and paraneoplastic retinopathy (CAR). Dermatomyositis is mentioned briefly. Not included are paraproteinemic neuropathies.

The clinical characteristics of the syndromes are not described, but referred to in text and tables. The tables point out the relationship between clinical syndrome, antibodies and related tumours. Screening is described for the tumours according to available literature. If no description was available, recommendations were based on screening strategies for this tumour in the general population or in high-risk patients.

Search strategies included English literature from Cochrane Database, MedLine and PubMed, using the keywords: 'LEMS', 'limbic encephalitis', 'sensory neuronopathy', 'autonomic neuropathy', 'cerebellar ataxia', opsoclonus-myoclonus', 'neuromyotonia', 'myasthenia gravis' and 'CAR' in combination with 'investigation' or 'screening'. Besides, search strategies using 'small cell lung carcinoma', 'thymoma', 'breast carcinoma', 'ovarian teratoma', 'ovarian carcinoma', 'testicular' 'Hodgkin's' in combination with 'paraneoplastic' and 'screening' were used. Also, the words 'Hu', 'CV2' or 'CRMP5' or 'CRMP-5', 'Yo', 'Ri', 'Ma2', 'amphiphysin', 'recoverin', 'Tr', 'VGCC' (voltage-gated calcium channels), 'acetylcholine', 'VGKC' (voltage-gated potassium channels), 'NMDA' (N-methyl-D-aspartic acid), 'AMPA' (α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate), 'GAD' (glutamic acid decarboxylase) and 'GABAR' (γ -aminobutyric acid

receptor) were used in combination with ‘paraneoplastic’ and ‘screening’. Only one study reached level III evidence [7], whilst all other studies contained level IV evidence. No level A, B or C recommendations could be made. However, good practice points were agreed by consensus, according to EFNS guidelines [12].

Screening for tumours in patients with PNS and paraneoplastic antibodies

When the diagnosis of a PNS is made, detection of the associated paraneoplastic antibody is of great importance as the type of tumour and the chance of an underlying malignancy depend mostly on the associated antibody. The relation between PNS, antibody and tumour are summarized in Tables 1 and 2. For a clinical description of the PNS, the reader is referred to the references in the tables, to extensive reviews [10,13–15] and to the EFNS Task Force Guideline: Management of PNS [11]. Screening is described by tumour.

A thorough history to determine risk factors and (sub)clinical complaints and examination, including examination of the pelvic region (rectal for prostate carcinoma in men; testicular in search for testicular tumours in men and gynaecological examination in women for ovarian tumours) and examination of the breast, is a requirement. As tumours can arise in many organs or body parts, thorough screening requires a multidisciplinary approach.

Small cell lung cancer

Small cell lung cancer was detected in 96% of SCLC-LEMS patients within 1 year [7]. Incidental reports of more than 2 years between onset of PNS symptoms and detection of SCLC are available, but most are reports before wide use of standard screening protocols and using inferior quality CT-scans [7,16–19]. One patient with an interval of 54 months is described whilst fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning was available [20], but this patient received chemotherapy at diagnosis of his paraneoplastic encephalomyelitis after the initial CT-scan was negative.

Screening by thoracic X-ray is insufficient as sensitivity is only 43%. CT-scan of the thorax showed a sensitivity of 83% at primary screening and 92% overall in patients with LEMS [7]. In a French study, conventional screening by X-ray and CT-thorax detected 71 of 85 SCLC (84%) in patients with PNS [20]; for 15 patients with an anti-Hu syndrome, described before, sensitivity of the same investigations was 80% [21]. In a German study of eight anti-Hu patients, CT-thorax detected only three of six tumours [22]. As one patient had a neuroblastoma, one developed the PNS on recurrence of the SCLC and the number of patients was small, we think it appropriate to estimate sensitivity of CT-thorax for SCLC in PNS to 80–85%.

FDG-PET has shown additional value in case series in comparison with CT-thorax. Because FDG-PET is only recently widely available, it has not been compared in large studies. Studies representing 19 patients with LEMS [7] and 13 patients with different PNS [22] directly compared CT-thorax to FDG-PET. Other studies investigated the use of FDG-PET after initial CT-thorax was negative in patients with different PNS [20,23,24]. All results showed additive effect of FDG-PET scans. Delay between initial CT-thorax and FDG-PET makes it impossible to determine accuracy of this combination in initial screening. Combined FDG-PET/CT-scanners might pose new opportunities, but data to support this are lacking.

Bronchoscopy provided no additional information in patients with LEMS if imaging revealed no abnormalities [7]. Often, the only abnormalities are in the mediastinal lymph nodes, so special focus should be aimed towards this region. Minimal invasive techniques, like Endoscopic UltraSound-guided Fine Needle Aspiration (EUS-FNA), reduce the need for mediastinoscopies and thoracotomies in SCLC (without PNS) with 70% [25].

Mediastinoscopy (and eventually thoracotomy) may be necessary sometimes to obtain histological or cytological diagnosis. The additional value of EUS-FNA, if imaging techniques are negative, is unknown.

Recommendation—Screen for SCLC by CT-thorax, followed by FDG-PET or integrated FDG-PET/CT (good practice point).

Thymoma

CT-thorax is currently considered first choice to screen for thymoma. Chest X-ray will merely show broadening of the mediastinum and is not as sensitive [26]. One retrospective study, directly comparing CT-thorax and MRI-thorax, showed sensitivity of CT-thorax to be at least equal to MRI [27]. CT-thorax showed moderate sensitivity (75–88%), but less specificity (42–81%); most problems arise distinguishing thymic hyperplasia (associated with early-onset myasthenia gravis) from thymoma [28]. Reliability in this study was lower than expected, most probably because of the long study period (1989–2003), as CT techniques developed rapidly during the study period. Difficulties to distinguish hyperplasia from thymoma were also detected in a Canadian study [29]. FDG-PET was helpful to distinguish thymic hyperplasia, thymoma and thymic carcinoma [30,31], as well as FDG-PET/CT [32].

Recommendation—Screen for thymoma by CT-thorax (followed by FDG-PET) or integrated FDG-PET/CT (good practice point).

Breast cancer

Mammography revealed breast cancer or infiltrated lymph nodes in 83% of patients with PCD, anti-Yo antibodies and breast cancer [8]. CT-thorax showed metastatic lymph nodes in the other two patients. Additional value of FDG-PET over mammography, ultrasound (US), CT and MRI has been described in patients with PNS in case reports and case series [20,33–35]. In one patient, diagnosis of breast cancer was made only 5 years after diagnosis of PCD, despite adequate repeated screening by CT chest/abdomen and FDG-PET [34].

Much research has focused on screening strategies in patients at high risk for breast cancer, but the subgroup with PNS has not been evaluated specifically. A Dutch prospective cohort study showed superior sensitivity of MRI (80%) vs. mammography (33%) in 1909 patients with a familial or genetic predisposition for breast cancer [36]. An American cohort study of 609 patients (asymptomatic, high-risk women with a negative mammogram before) compared mammography, US and MRI during the next 2 years. Breast cancer was found in 18 patients, and the sensitivity was 44%, 17% and 71%, respectively [37]. Five other prospective cohort studies compared MRI with mammography and US in women with a lifetime risk for breast cancer over 20–25% showed similar results: sensitivity was 77–100% for MRI, 16–40% for mammography and 16–40% for US [37]. Recent American guidelines for breast screening recommended MRI-breast screening as an adjunct to mammography in women with a lifetime risk over 25% [38,39].

Recommendation—Screen for breast cancer by mammography, followed by MRI-breast. If negative followed by FDG-PET/CT (good practice point).

Ovarian teratoma and carcinoma

The optimal modality to screen the ovaries will depend on the expected tumour: carcinoma in anti-Yo, anti-Ri and anti-amphiphysin-related PNS and teratoma in anti-NMDAR related PNS.

Teratoma—The majority of teratomas are mature cystic teratomas (MCT). Immature teratomas (IT), constituting 1% of all teratomas, were present in 29% of anti-NMDAR-related cases [5]. Bilateral teratomas were present in 14% [5], comparable to 12% described in general [40]. US showed a MCT with a highly variable sensitivity of 58–94% [40]. IT are more difficult to differentiate by US [40]. Most studies have used transvaginal (TV) US, but a direct comparison of TV and transabdominal (TA) US has not been performed. CT showed a very good sensitivity of 93 [41] to 98% [42]. The only direct comparison of (TV) US and CT showed a better sensitivity for CT: 93 vs. 79% [41]. MRI has also a very good sensitivity of 93–96% [43]. FDG-PET has not been studied in teratomas, but MCT have no or little uptake of fluorodeoxyglucose (FDG). FDG-PET is not expected to be sensitive for teratomas. An advantage of CT over US is that extra-pelvic teratomas (occasionally described as anti-NMDAR-related teratomas) can also be detected [5]. Transvaginal US followed by CT or MRI is the investigation of choice [10]. In young patients, MRI may be first choice to avoid radiation by repeated CT.

Recommendation—Screen for ovarian teratoma by TV US, followed by CT/MRI-pelvis/abdomen. If negative, followed by CT-thorax (good practice point).

Ovarian carcinoma—Ultrasound is the investigation of first choice to detect ovarian carcinomas. TV US is a more sensitive investigation than TA US [44]. Sensitivity for ovarian carcinoma was 85% in medium to high-risk patients [45]. A meta-analysis by Liu *et al.* [46] compared US, CT and MRI showing similar results with sensitivities of 89%, 85% and 89%, respectively. The current NCCN Clinical Practice Guidelines in Oncology recommend TV US, combined with cancer antigen 125 (CA-125) each 6 months in patients with a genetic/familial high risk for ovarian carcinoma [39]. Integrated FDG-PET/CT has been studied only to detect the recurrence of ovarian carcinoma or in patients selected by abnormal US or markedly raised CA-125. A few case reports describe an additional value of FDG-PET in such patients [20,22,33,47]. Even if screening revealed no malignancy, surgical exploration and removal of ovaries has been suggested in patients with anti-Yo cerebellar degeneration and worsening neurological status, especially in post-menopausal women [48]. Although the neurological condition does not ameliorate by surgery, diagnosis and treatment of the primary tumour may improve survival. Besides, the neurological symptoms can stabilize, especially in moderately affected patients [49].

Recommendation—Screen for ovarian carcinoma by TV US, followed by CT-pelvis/abdomen or integrated FDG-PET/CT (good practice point).

Testicular tumours

Ultrasound investigation of the testicular region detected 18 (72%) of 25 testicular tumours [50]. CT-scan of the pelvic region added one patient. FDG-PET-scanning had no additional value in the two patients tested. This study showed that it has additional value to obtain tissue (biopsy or orchiectomy, unilateral or even bilateral) in young male patients (<50 years) with anti-Ma2 antibodies, deteriorating neurological disease and microcalcifications on US.

Recommendation—Screen for testicular tumour by US, followed by CT of the pelvic region (good practice point).

Other tumours

Other tumours like Hodgkin's lymphoma, small cell prostate carcinoma and neuroblastoma (in children) have been described in relation to paraneoplastic disorders. All reports describe single cases or small series, with little relevance for screening recommendations.

Screening for tumours in possible PNS without identified paraneoplastic antibodies

The recommendations for screening for tumours in patients with a possible PNS, but without detectable antibodies are less clear. Mason *et al.* [51] described 57 cases with PCD and SCLC. This study concluded that almost half of the patients had ‘no antibodies’, but only anti-Hu and anti-VGCC antibodies were examined. As listed in Table 1, also other antibodies can be found in PCD.

Two studies report the use of FDG-PET in PNS with and without known antibodies. Rees *et al.* [24] found only 46% of patients to have anti-Hu or anti-Yo antibodies. As most patients presented with non-classical PNS or with syndromes related to other antibodies (for example brainstem encephalitis and LEMS), this percentage is not useful for routine clinical practice. Hadjivassiliou *et al.* [23] described FDG-PET in 80 patients with negative whole-body CT-scan. They found four patients with a classical PNS, no antibodies and a pathological proven tumour. One patient had clinical LEMS, in which a screening is warranted. In three other patients, it is not clear if all relevant antibodies had been tested. As whole-body CT was negative, it was a highly selected group and percentages of antibody negativity cannot be extrapolated to clinical practice.

Recommendation—If no antibodies are found, the patient has a classical PNS and the neurological condition is deteriorating, screening according to the most likely site, guided by the type of PNS with conventional methods, and if negative by total-body FDG-PET, is recommended (good practice point).

Dermatomyositis

The reported frequency of malignancy in dermatomyositis varies from 6% to 60%, but large population-based cohort studies report a frequency of 20–25% [52]. No particular paraneoplastic antibodies have been described for dermatomyositis. Several cancer types show this association. The most common are ovarian, lung, pancreatic, stomach and colorectal cancers and lymphomas [53]. The risk for lymphoma was only raised the first year after diagnosis of dermatomyositis. For the other tumours, the risk is the highest within the first year of follow-up dropping substantially thereafter. The risk for ovarian, pancreatic and lung cancer remains above average even after 5 years [53]. At diagnosis, thorough examination is requested. In children, specific attention should be paid to splenomegaly or lymphadenopathy [54]. In adults, abnormalities should guide screening tactics, but lack of abnormalities does not imply no screening is needed. Although the risk rises with age, all adult patients should be screened. Women should be screened by US of the pelvic region and mammography and by CT-thorax/abdomen. Men should be tested by CT-thorax/abdomen. Men under the age of 50 years should have an US of the testes. All patients over 50 years old (men and women) should have a colonoscopy. Screening is to be repeated annually for 3 years. Afterwards, screening is only performed if new symptoms or findings alert to it [52,55]. Evidence regarding any additional value of FDG-PET is lacking.

Recommendation—Screen all adult patients with dermatomyositis by CT-thorax/abdomen. Women are tested also by US of the pelvic region and mammography. Male patients under 50 years old should have US of the testes. Patients over 50 years old should have a colonoscopy (good practice point).

Use of clinical information and laboratory investigations in screening

The combination of a clinical syndrome and an associated antibody is the most powerful predictor for an underlying tumour and its possible location. As most syndromes and tumours are related to more than one antibody, screening for a panel of antibodies is more fruitful than focusing on one specific target [56]. Within the clinical syndromes, no specific

predicting factor can be assigned to discriminate between tumour and non-tumour forms. A more severe clinical picture has been described in SCLC-LEMS patients [57,58], but the specificity is not high enough to be helpful in individual patients.

Recommendation—As most clinical PNS are not specifically related to one antibody, testing for several paraneoplastic antibodies simultaneously will improve the yield, avoiding loss of time before a malignancy is detected (good practice point).

Biomarkers—Paraneoplastic antibodies are related to different PNS (Table 2). The individual antibodies are referred to in this table, but are not described in detail in this paper. Other antibodies are not related clinically to specific PNS, but have been described as specific biomarkers, like SOX1 antibodies for SCLC. SOX1 antibodies were present in 22–32% of SCLC patients without PNS [59–61]. In SCLC-LEMS patients and SCLC-PCD patients (with VGCC antibodies), SOX1 antibodies were present in 65% and 67%, respectively. In patients with SCLC and anti-Hu syndrome, antibodies were present in 32–40% of sera [59,60]. Only two patients with LEMS without SCLC were positive, whilst none of 80 controls were. Although sensitivity is low to moderate, specificity is high and seropositivity indicates a very high suspicion of an underlying tumour. Case series described two patients with PLE, SCLC and VGKC antibodies to be positive for SOX1, whilst seven patients with SCLC-PLE without VGKC antibodies and seven patients with a non-tumour PLE with VGKC antibodies were SOX1 negative [62]. One patient with PLE, SCLC and GABA_BR antibodies had SOX1 antibodies, whilst six other patients with GABA_BR antibodies, PLE and a tumour and eight patients without tumour were SOX1 negative [63]. No data are available for other syndromes or other tumours related to PNS.

Anti-titin antibodies are a sensitive marker for thymoma (69–95%) [64–66], but not specific. Although only 8–10% of early-onset patients with MG are positive for anti-titin antibodies, 58–78% of late-onset patients with MG are positive [64,65]. RyR antibodies are more specific (95%), but a less sensitive marker (70%), in direct comparison to anti-titin antibodies [65].

Neuron-specific enolase (NSE) has been the tumour marker of choice in SCLC. Sensitivity was 65% in a cohort of 175 SCLC patients (without PNS), but depended on tumour stage [67]. Sensitivity was only 54% in limited disease patients with SCLC (vs. 74% in patients with extended disease). Awareness of a tumour is better in patients with PNS, which are found to have more limited disease [7], limiting the value of NSE. Progastrin-releasing peptide (ProGRP) is another, relatively new, marker for SCLC. Sensitivity is better than for NSE (77%) and does not differ between patients with limited or extended disease (74% vs. 78%) [67]. Unfortunately, ProGRP is not routinely available yet. Both markers have not been investigated in PNS.

CA-125 is a marker for ovarian cancer. Although serial serum values detect up to 86% of ovarian carcinomas in post-menopausal women [68], a single CA-125 value has a sensitivity of only 62% [68]. In MCT, CA-125, cancer antigen 19–9 (CA19-9), alpha-fetoprotein (AFP) and carcinoembryonic antigen were elevated in 23%, 39%, 0.6% and 16%, respectively [69]. In immature teratomas, AFP is raised in up to 50% of cases [40].

The beta-subunit of the human chorionic gonadotropin (β -HCG) and AFP are elevated in about 80% of non-seminomatous testicular cancers [70]. It is recommended to determine β -HCG and AFP in patients with suspected testicular tumours [71]. In the limited number of paraneoplastic cases where US was unreliable, β -HCG and AFP were also negative [50].

Recommendation—Positive tumour markers raise suspicion of a tumour, but normal values do not exclude malignancy as sensitivity is low to moderate (good practice point).

Repetition of screening if initial screening is negative

Current recommendation is to repeat screening regularly every 6 months up to 4 years in patients with PNS and paraneoplastic antibodies [11]. First repetition of screening should be carried out after 3 or 4 months if suspicion of a malignancy remains high. In patients with LEMS, a large cohort study shows that 2 years of screening is sufficient [7]. Screening by thoracic X-ray or tumour markers is not reliable.

Recommendation—If initial screening is negative in a patient with PNS and paraneoplastic antibodies, second screening should be repeated after 3–6 months, followed by regular screening every 6 months for 4 years. In patients with LEMS, 2 years is sufficient. X-ray or blood sampling is not reliable (good practice point).

Recommendations/Good practice points

1. Nature of antibody, and to a lesser extent the clinical syndrome, determine the risk and type of an underlying malignancy.
2. As most PNS are not specifically related to one antibody, testing for several paraneoplastic antibodies simultaneously will improve the yield, avoiding loss of time before a malignancy is detected.
3. Screen for SCLC by CT-thorax followed by FDG-PET or integrated FDG-PET/CT.
4. Screen for thymoma by CT-thorax (followed by FDG-PET) or integrated FDG-PET/CT.
5. Screen for breast cancer by mammography, followed by MRI-breast. If negative followed by FDG-PET/CT.
6. Screen for ovarian teratoma by TV US, followed by CT/MRI-pelvis/abdomen. If negative, followed by CT-thorax.
7. Screen for ovarian carcinoma by TV US and CA-125, followed by CT-pelvis/abdomen or integrated FDG-PET/CT.
8. Screen for testicular tumour by US, β -HCG and AFP, followed by CT of the pelvic region. Biopsy is recommended in men under the age of 50 with classical PNS and microcalcifications on US.
9. If tumour screening is negative and the neurological condition is worsening, exploratory surgery and eventually preventive removal of the ovaries is warranted in post-menopausal women with an anti-Yo-associated PNS.
10. Additional laboratory investigations have extra value if the antibody and the associated PNS are related to both a paraneoplastic and a non-paraneoplastic subtype (like LEMS and myasthenia gravis). Positive markers raise suspicion of a tumour, but normal values do not exclude malignancy as sensitivity is low to moderate.
11. If no paraneoplastic antibodies are found, the patient has a classical PNS and the neurological condition is deteriorating, screening according to the most likely site, guided by the type of PNS with conventional methods, and if negative by total-body FDG-PET, is recommended.

12. Screen all adult patients with dermatomyositis by CT-thorax/abdomen. Women should be tested also by US of the pelvic region and mammography. Male patients under 50 years old should have US of the testes. Patients over 50 years old should have a colonoscopy.
13. If initial screening is negative in a patient with PNS and paraneoplastic antibodies, screening should be repeated after 3–6 months, followed by regular screening every 6 months for 4 years. In patients with LEMS, 2 years is sufficient. X-ray and tumour markers are not reliable.

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Table 1

Paraneoplastic syndromes and their associated antibodies and tumours. The most frequent antibodies and tumours are listed in bold

Neurological syndrome	Antibody	Tumour	References
Encephalomyelitis/limbic encephalitis	Anti-Hu, anti-Ma2 , anti-CV2/CRMP5, anti-VGKC, anti-Ri, anti-amphiphysin, anti-GABA _B R, anti-AMPA, anti-GAD	SCLC, testicular tumour , thymoma, neuroblastoma, prostate carcinoma, breast cancer, Hodgkin's lymphoma	[6,50,63,72–75]
Cerebellar degeneration	Anti-Yo, anti-Hu , anti-VGCC, anti-CV2/CRMP5, anti-Ma2, anti-Ri, anti-Tr, anti-GAD, anti-mGluR1- α	SCLC, ovarian cancer, breast cancer, Hodgkin's lymphoma , thymoma	[8,48,51,76,77]
Brainstem encephalitis/opsoclonus-myoclonus	Anti-Ri, anti-Ma2 , anti-Hu, anti-amphiphysin	Breast cancer, ovarian cancer, testicular tumour, SCLC, neuroblastoma (children)	[50,78]
Encephalitis with psychiatric manifestations, seizures, dyskinesias, dystonia and autonomic instability	Anti-NMDAR	Ovarian teratoma , testis teratoma, SCLC	[5,79]
Neuromyotonia	Anti-VGKC	Thymoma, SCLC	[19]
Lambert-Eaton myasthenic syndrome	Anti-VGCC	SCLC	[80]
Myasthenia gravis	Anti-AChR	Thymoma	[81]
Subacute sensory neuropathy	Anti-Hu , anti-CV2/CRMP5, anti-amphiphysin	SCLC , breast cancer, ovarian cancer	[6,82]
Subacute autonomic neuropathy	Anti-gAChR, anti-Hu	SCLC , thymoma	[82]
Stiff-person syndrome	Anti-amphiphysin , anti-GAD	Breast cancer , SCLC	[83–86]
Cancer-associated retinopathy	Anti-recoverin	SCLC , endometrium cancer	[87–89]

SCLC, small cell lung cancer.

Table 2

Paraneoplastic antibodies in relation to the associated neurological syndromes and tumours. The most frequently associated tumour type is given in bold.

	Tumour present (%) [90]	Neurological syndrome	Tumour	References
Antibodies to non-surface antigens in PNS				
Anti-Hu (ANNA-1)	98	Encephalomyelitis, limbic encephalitis, sensory neuropathy, cerebellar degeneration, autonomic neuropathy	SCLC , neuroblastoma, prostate cancer	[6,20,22,51,82,91,92]
Anti-Yo (PCA1)	98	Cerebellar degeneration	Ovarian carcinoma , breast cancer	[8,20,47,48,77]
Anti-CV2/CRMP5	96	Cerebellar degeneration, sensory (motor) neuropathy, chorea, limbic encephalitis, encephalomyelitis, optic neuritis	SCLC, thymoma	[20,92-94]
Anti-Ma2 (anti-Ta)	96	Limbic encephalitis, brainstem encephalitis, cerebellar degeneration	Testicular tumour (males <50 year) , lung cancer, breast cancer	[50,72,95]
Anti-Ri (ANNA-2)	97	Opsoclonus-myoclonus, brainstem encephalitis, cerebellar degeneration	Breast cancer, SCLC , gynaecological tumours	[77,78,96,97]
Anti-amphiphysin	95	Stiff-person syndrome, encephalomyelitis, sensory (motor) neuropathy	Breast cancer, SCLC , ovarian cancer	[83-85,97]
Anti-recoverin	99	Cancer-associated retinopathy	SCLC , endometrium cancer, thymoma, prostate cancer	[87-89]
Anti-Tr	89	Cerebellar degeneration	Hodgkin's lymphoma	[22,76,98,99]
Anti-GAD	8 ^a	Cerebellar degeneration, limbic encephalitis, stiff-person syndrome	SCLC, lung cancer, thymic cancer, pancreatic cancer, renal cell cancer	[75,86]
Antibodies to surface antigens in PNS				
Anti-VGCC	55	Lambert-Eaton myasthenic syndrome	SCLC	[51,80,100]
Anti-AChR	15	<i>b</i> Cerebellar degeneration	Thymoma	[81]
Anti-gAChR	15	Myasthenia gravis	SCLC , thymoma	[101,102]
Anti-NMDAR	9-56	Autonomic neuropathy	Ovarian teratoma , testicular teratoma	[5,79]
Anti-VGKC-related proteins (LGII, CASPR2)	25-31	Encephalitis with psychiatric manifestations, seizures, dyskinesias, dystonia and autonomic instability	Thymoma, SCLC	[19,103,104]
Anti-GABA _B R	47	Limbic encephalitis	SCLC , lung tumour	[63]
Anti-AMPA	70	Limbic encephalitis	Thymoma, lung cancer, breast cancer	[74]
Antibodies, reported in case reports				
Anti-mGluR1- α		Cerebellar degeneration	Hodgkin's lymphoma	[105]

	Tumour present (%) [90]	Neurological syndrome	Tumour	References
ANNA-3		Encephalomyelitis, sensory neuropathy	SCLC	[106]
PCA-2		Encephalomyelitis, cerebellar degeneration	SCLC	[107]
Anti-Zic4		Cerebellar degeneration	SCLC	[108]

^a Possible anti-GABA_BR related.

^b Almost invariably with tumour.

PNS, paraneoplastic neurological syndromes; SCLC, small cell lung cancer.