Neuro-oncology Neurotoxicology

P 2105

Hu and VGCC antibodies related to the prognosis of small-cell lung cancer

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Introduction Hu antibodies have previously been associated with longer survival of patients with small-cell lung cancer (SCLC). VGCC antibodies play a pathogenic role in the Lambert Eaton myasthenic syndrome (LEMS) which is also associated with SCLC, and these antibodies may reduce tumour growth. We tested a large cohort of sera from SCLC patients to see whether Hu and VGCC antibodies correlated with better SCLC prognosis.

Method 200 patients with SCLC (age 39–79, mean 62.3 years; 129 males and 71 females) receiving similar treatment were studied. Sera from these patients were examined for Hu antibodies by an immunoprecipitation assay and by imunohistoche-

mistry/Western blot. VGCC (P/Q subtype) antibodies were detected by radioimmunoassay. Survival analysis was used to evaluate the data.

Results Hu antibodies were detected in 51/200 (25.5%) by immunoprecipitation and 37/200 (18.5%) by immunohistochemistry/Western blot, whereas VGCC antibodies were detected in only 10/200 (5%) of the patients. Hu antibodies did not correlate with VGCC antibodies, and there was no association between Hu or VGCC antibodies and the extent of the disease, metastatic sites or survival.

Conclusion Hu and VGCC antibodies are found in a proportion of SCLC patients, but their presence does not correlate with the prognosis of the SCLC, and they probably do not suppress tumour growth.

P 2106

Pyramidal cell antibodies associated with limbic encephalitis and thymoma

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Introduction Paraneoplastic neurological syndromes are rare, but very disabling neurological diseases that arise as remote effects of several different tumours. Thymoma can be associated with various antibodies such as anti-AChR, anti-titin, anti-RyR, anti-VGKC and anti-CV2. We report a new paraneoplastic antibody that may be related to thymoma.

Methods A 52-year-old patient developed limbic encephalitis with focal epileptic seizures. Screening for occult cancer revealed a thymoma. Paraneoplastic antibodies related to limbic encephalitis such as anti-Hu, anti-amphiphysin, anti-Ta, anti-CV2, anti-Ri and those related to thymoma as mentioned above were negative. Serum from this patient and from 10 patients with thymoma and myasthenia gravis were examined for antibodies against hippocampal antigens by immunohistochemical methods.

Results Serum from the patient with limbic encephalitis and thymoma stained hippocampus from rat brain. Furthermore, confocal immunofluorescence studies showed that axonal boutons and growth cones of hippocampal neurons in culture were distinctly labelled, colocalizing with the vesicle marker synaptophysin. Western blot of rat brain extract revealed a band of approximately 60 kDa. Such antibodies were not detected in the sera from 10 other patients with thymoma.

Discussion We describe a new possible paraneoplastic antibody against pyramidal cells that may be associated with limbic encephalitis and thymoma.

P 2107

Inhibition of human glioma cell growth by a PHS-2 inhibitor, NS398, and a prostaglandin E receptor subtype EP1 selective antagonist, SC51089

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Introduction Prostaglandin H synthase (PHS) is a key enzyme in the synthesis of prostaglandins (PGs). Recently, enhanced expression of PHS-2 in brain tumours and its correlation to the histopathological grade of glioma has been reported. Furthermore, *in vitro* inhibition of growth of glioma cells by a specific PHS-2 inhibitor, NS398 has been demonstrated. It was also

shown that PGE₂ contribute colon carcinogenesis through its binding to the prostaglandin E receptor subtype EP1. We therefore evaluated the effect of a specific PHS-2 inhibitor, NS398, and EP1 antagonists, SC51089 and AH6809, on glioma cell lines

Methods Two glioma cell lines, one is PHS-2 positive cell line (KMG4) and the other is PHS-2 deficient cell line (A172), were used. To evaluate anchorage-dependent growth, 5-Bromo-2'-deoxy-uridine (BrdU) labelling and detection kit III (Boehringer Manheim) was used, while colony forming assay was used for anchorage-independent growth. *In vivo* tumour growth was assessed using KMG4 tumour xenografts on SCID mice.

Results NS398 inhibited anchorage-dependent and -independent growth of glioma cell lines regardless of PHS-2 expression, suggesting there are some PHS-2 independent mechanisms for antineoplastic effect of NS398. However, the antineoplastic effect was attenuated by addition of PGE₂, which is one of the main products of PHS, suggesting that the predominant mechanism is PHS dependent. EP1 antagonists, SC51089 and AH6809, inhibited the growth of glioma cell lines *in vitro*. Furthermore, NS398 or SC51089 slowed tumour growth *in vivo*.

Conclusion PHS-2 inhibitors and EP1 antagonists might be useful in the prevention and/or treatment of glioma.

P 2108

Changes in EEG photic driving in workers exposed to mercury vapours

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Objective To study photic driving (PD) in workers exposed to mercury.

Subjects and methods 24 workers from a chloralkali plant exposed to mercury (mean age 42 yrs, mean duration of exposure 15 yrs); 24 matched controls. Mean air-borne concentration of Hg at workplace 59 μ g/m³. Mean urinary excretion of Hg 64.3 μ g/24 hours spontaneously, and 751.9 μ g/48 hours after mobilization by sodium 2.3-dimercapto-1-propan sulfonate. Photic stimulation included frequencies 1–30 Hz.

Results The number of stimulation frequencies eliciting PD was higher in the exposed group, compared to the controls (median 17 and 10 frequencies, respectively; p<0.001). The maximum value of PD was higher in the exposed than in the control group (median 24.6 and 9.4 z-units, respectively; p<0.001). The median stimulation frequency with maximum driving was 15 Hz in the controls and 20 Hz in the exposed (p<0.01). The median sum of PD and the median index of PD were higher in the exposed than in the controls (p<0.01). The increased PD was mainly at high stimulation frequencies. There was no significant association between PD and exposure.

Conclusion PD is generated in the visual cortex. Mercury shows predilection for this structure. An increased PD is regarded as a sign of nervous system hyperexcitability (e.g. in migraine). Consequently, the increased PD in exposure to Hg could be interpreted as a marker of neuronal hyperexcitability due to an early neurotoxic effect of Hg.

Acknowledgment: The study was supported by grants IGA 5153-3, 4510/3, and NE/6222-3.

P 2109

Neurological and neurophysiological examinations of workers occupationally exposed to aluminium.

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Introduction Numerous studies are conducted to assess aluminium (Al) -induced toxicity to humans and environment. It has been implicated in the aetiology of Alzheimer's disease and other neurodegenerative disorders, though it is controversial. The aim of the present study was to assess the effects of aluminium on the functions of the nervous system in workers chronically exposed to this metal.

Methods The study covered a selected group of 67 male workers (mean age 38.7 ± 10.3) involved in the aluminium production. Their employment duration ranged between 2 to 33 yr (mean 14.6 ± 10.3). Aluminium oxide (Al₂0₃) concentrations varied from 0.2 to 2 mg/m³ (arithmetic mean -0.40 mg/m³, geometric mean -0.35 mg/m³, standard deviation -0.29). The control group consisted of 57 men non-occupationally exposed to Al, matched by sex, age and work shift distribution.

Results Clinically, the headache, increased emotional irritability, concentration difficulties, sleeplessness and mood swings predominated among the disorders of the nervous system functions in workers chronically exposed to Al. The objective neurological examinations did not reveal organic lesions in the central or peripheral nervous system. Generalized and paroxysmal changes were most common recordings in the abnormal electroencephalography (EEG). Visual evoked potentials (VEP) examinations revealed abnormalities, primarily in the latency of the response evoked.

Conclusion The results of this study suggest that Al203 exposure to concentrations within MAC values produce subclinical health effect in the nervous system.

P 2110

Nervous system dysfunction among workers with long-term exposure to manganese

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Introduction Manganese (Mn) affects primarily the nervous system. Cases of grave damages have not been reported, and neurological examinations are focused on detecting early symptoms. Aim of our study was to assess nervous system health effects in workers of the shipbuilding and electrotechnical industries exposed to manganese.

Methods Tests were performed on a group of male workers (welders and fitters), aged 20 to 56 years (mean 39.17+9.79 years). Period of employment ranged from 1 to 41 years, mean 17.5+10.8 years. Air Mn concentrations during welding ranged from 0.004 mg/m³ to 2.67 mg/m³, and the MAC value of 0.3 mg/m³ was exceeded in 36 subjects. Values of the cumulative dose index ranged between 0.28 and 35.5, mean 8.37+6.48. Control group comprised 62 non-exposed males matched for age and work shifts to the exposed group. Neurological examination included subjective and objective examinations of the nervous system, electroencephalographic (EEG) and visual evoked potential (VEP) evaluations.

Results Neurological symptoms noted in the exposed group comprised states of emotional arousal, impaired memory and concentration, excessive sleepiness during daytime, paraesthesia in the extremities. Neurological examinations did not reveal any systemic changes in the central nervous system for diagno-

sing clinical encephalopathy or neuropathy. Generalised and paroxysmal changes dominated among abnormal EEG records. VEP tests revealed abnormalities in the evoked response, which may point to visual neuron disorders.

Conclusion Our results suggest the exposure to manganese within, or slightly above, the MAC (arithmetic mean – 0.389 mg/m³, geometric mean 0.154 mg/m³) value causes subclinical health effects in the nervous system.

P 2111

Electroencephalographic findings in adolescents with glue sniffing

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Introduction There are many case reports on severe central nervous system (CNS) effects of toluene in glue sniffers. The aim of this study was examine the effects of toluene in glue sniffers on the EEG in search of a central neurological dysfunction.

Methods We were tested 17 boys who were glue sniffers. A brief history of every subject was taken, and general physical and neurological examinations were performed. They had no clinical findings of neurological disorders by the examination. Haematological parameters, serum liver enzyme activities, and renal values of all subjects were within normal limits. The EEGs were recorded when patients were awake in daytime.

Results The ages of the subjects ranged from 13 to 18 years (mean, 15.4 years). They had quitted the habit at least one month ago (range 1 to 3 months, mean 2.3 months). The duration of the abuse before rehabilitation ranged from two to five years, with a mean of 3.1 years. The EEGs were normal in seven subjects. Abnormal EEG was observed in 58.8% (n=10) of all the subjects. Seven subjects had various focal and/or diffuse EEG abnormalities.

Conclusions The changes of EEG are a sensitive measure of the effects of toluene on the CNS. However, the EEG results are not homogeneous for toluene abusers in all studies, as well as in our study. Therefore, we suggest that EEG may be useful addition to other clinical, laboratory and radiological means of examining toluene affecting the nervous system.

P 2112

Neurotoxicity of tributyltin in Sprague-Dawley rat brain C. Soo Youn¹, S. Chi Won¹, O. Jae Ho¹, P. Ki Sook¹, P. Sung Gyu¹, H. Jin Tae², P. Chang Won¹, J. Hae Kwan¹, Y. Ki Hwa¹ Department of General Toxicology, National Institute of Toxicological Research, Seoul, REPUBLIC OF KOREA, ²College of Pharmacy, Chungbuk National University, Cheongju, REPUBLIC OF KOREA

Introduction The organotins such as tributyltin (TBT) are used mainly in wood preservation, marine antifouling paints, disinfection of circulating industrial cooling waters. There were also some reports indicating that the exposure to organotin compounds causes epilepsy and amnesia in human and experimental animals. However, neurotoxic effect and its mechanism were not fully understood. Therefore, we investigated the neurotoxic effect and mechanism of TBT in SD rats.

Methods 8 week-old male SD rats were treated orally TBT (0, 1, 3, 5 mg/kg/day) for 7 days. And other groups were treated orally TBT (10mg/kg) for single dose. The locomotor activity and immunohistochemical changes were examined.

Results We found slightly body weight loss in the group of 3.5mg/kg/day treatment. The distance travelled of TBT treated rats were decreased but resting time was slightly increased in a

dose-dependent manner. The number of tyrosine hydroxylase immunoreactive (TH-IR) neurons in SN and VTA, and processes in the compacta part and reticulosa part of SN was slightly decreased of TBT-treated rats in a dose-dependent manner. However, COX-2 IR cell numbers were increased in a dose-dependent manner in same regions. The GABA and calmoduin-IR cell numbers in Purkinje cells of cerebellum of 3 and 5mg/kg/day TBT treated groups were decreased, and single dose TBT treated groups were also decreased in 1, 3, 5 day but increased in 2 week. However, COX-2 was not expressed in the Purkinje cells of cerebellum.

Conclusions The dopaminergic neuron has inflammatory pathway and the Purkinje cell has calcium mediated apoptosis pathway by TBT treatment.

P 2113

Alcoholism: acute and chronic neurological complications in 420 patients

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Objective To evaluate type, incidence and severity of alcohol related neurological disturbances.

Materials We studied 420 patients (pts), 225 males and 195 females, mean age 48.8 years, with anamnestic history of alcohol abuse for more than five years. All pts were treated in Neurological Department in the last 10 years in acute intoxication phase or for chronic neurological complications. All pts underwent clinical examination, routine blood laboratory tests (including alcoholemia and ammonemia), EEG, EMG, brain CT scan, psychologic interview, neuropsychological tests and hepatic echography.

Results 84 pts, 54 males and 30 females, had more epileptic generalized seizures. The EEG was normal in 300 pts, with diffuse abnormalities in 85 and focal abnormalities in 30. Brain CT scan showed evidence of brain atrophy in 175 cases, with neuropsychological tests indicative for dementia in 25 pts (15 males and 10 females). The EMG showed a sensory-motor polyneuropathy in 329 pts.

The pts treated for an acute abstinence syndrome were 79.5%; among these 20% presented generalized epileptic seizures and 27.3% delirium tremens. The pts that presented as chronic complication a sensory-motor polyneuropathy of various severity (78.3%) were affected also by behavioural disturbances in 10% of cases, by alcoholic dementia in 6%, by Korsakow syndrome in 1.2% and by hepatic encephalopathy in 15%.

Conclusion From our study emerges a high incidence of hospitalisation for acute and chronic alcohol correlated neurologic pathologies with the presence of severe biologic complications that cause an elevated social-sanitary cost of the alcoholism.

P 2114

Excitatory effect of B-n-methylamino-l-aspartate on retzius nerve cells of the leech haemopis sanguisuga

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Excitatory amino acid b-N-methylamino-L-aspartate (BMAA) is present in the plant Cycas circinalis, which is used in food and medicine by the population of western pacific region. That EAA

has been implicated in the pathogenesis of human neurodegenerative disorder western pacific amiotrophic lateral sclerosisparkinsonism - dementia complex (ALS/PDC). Since Retzius cells posses glutamate receptors, we investigated the effect of L-BMAA on these cells. Intracellular recordings were made using glass tube microelectrodes filled by 3M KCl, with resis-tance of 5-15 M Ω . In our experiments average value of resting membrane potential was 51.2±25.8 mV (n=5). Bath application of L-BMAA (obtained from Prof P.S. Spencer, Oregon Health Sciences University, Portland, USA) in concentration of 10⁻² moll/l during 3 min elicited depolarisation. Average value of that depolarisation was 12.0±6.1 mV (n=5). Our experiments indicate that L-BMAA has excitatory effect on Leech Retzius nerve cells. We compared this effect to the effects of β-N-oxalylamino-L-aspartate (L-BOAA) and L-Aspartate (L-Asp) from our previous experiments on the same experimental model (1), and concluded that the effect of 10⁻² moll/l L-BMAA is comparable to the effects of 10⁻² L-Asp and $5x10^{-5}$ moll/l L-BOAA. This indicates that L-BMAA is similar in potency to L-Asp, and approximately 500 times less potent then L-BOAA in our experimental model.

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P 2115

Nitrile neurotoxicity as model of human neurodegenerative diseases

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Nitriles are a large family of compounds, and humans are routinely exposed to both industrial and natural nitriles. Their toxic properties include acute lethality and osteolathyrism. In addition, a number of nitriles have neurotoxic effects. However, these effects are not well understood, and the potential for neurotoxicity of nitriles as a class has not been established. 3.3'-Iminodipropionitrile (IDPN) has been mostly studied as an agent causing a neurofilamentous proximal axonopathy, as observed for ALS disease. However, IDPN neurotoxicity was first known to cause permanent alterations in motor behaviour, an effect that remained unexplained in the early 90's.

Current evidence from our research group indicates that IDPN mainly affects the sensory systems, including the retina and the cornea, the olfactory mucosa, and the auditory and vestibular sensory epithelia. The vestibular toxicity is particularly relevant because it offers an explanation for the effects of IDPN on motor behaviour and as model of aminoglycosidic antibiotics toxicity. This sensory toxicity is also caused by other nitriles, including allylnitrile and cis-crotononitrile. The neurofilamentous axonopathy has only been demonstrated for IDPN. Thus nitriles show overlapping but not identical neurotoxic properties, and many of these rely on the nitrile group and do not require neither two nitrile groups nor the imino group that are exclusive to the IDPN molecule. Likewise, there are some similarities between their effects in vivo and some human neurodegenerative diseases, like neuropathic ataxia or spastic paraparesis, and can be used as models for studying ototoxicity or dizziness, apart of their industrial exposure interest.

P 2116

Successful therapy of oligodendroglioma seeding in the CNS by combined long-lasting intrathecal (i.th.) and systemic chemotherapy

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A female (28yrs) 1989 was operated upon a right frontal oligodendroglioma. Local relapses in 1992 and new, remote relapses in 8/1994 were successfully treated with stereotactic RT. 3 new local lesions were re-operated in 10/1995. After presentation in our institution we conducted 4 cycles of PCV until 7/1996 and the pt. stabilized till 2/1997 when again a right frontal relapse occurred being treated again by stereotactic seed. 4/1998 3 new remote recurrences were diagnosed in the left frontal and temporal cortex corresponding to CSF dissemination. Atypical cells were present in CSF. I.th. Ara-C was started combined with 5 cycles ACNU+VM26 and 11/1998 CR was achieved with negative CSF and C11-Methionin-PET. I.th. Ara-C was continued until 5/1999 amounting to 27 injections with a total dose of 1580mg. 7 months after discontinuation in 12/1999 2 new CSF born metastases occurred left frontal/insula. I.th. Ara-C was resumed (again 27 injections with 1140mg total dose) and 8 cycles Temozolomide administered resulting in a new CR (10/2000). A final relapse in 1/2001 was unresponsive to further chemotherapy and now after a total dose of 2840mg Ara-C i.th. in conjunction with the preceding therapies neurotoxic ataxia occurred and Ara-C was stopped. A slowly progressive cognitive, particular memory decline was seen in the last 2 years.

Conclusion It is important to differentiate multifocal/multiple gliomas from secondary parenchymatous involvement from meningeal metastases since additional intrathecal chemotherapy may be an effective treatment, and prophylaxis of further seeding. Long-lasting i.th. Ara-C treatment is possible without obvious neurotoxicity.

P 2117

Multiple central nervous system amyloidomas

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Introduction Amyloidomas rarely involve the Central Nervous System (CNS) and they are unrelated to systemic amyloidosis. CNS lesions either solitary or multiple invariably involve white matter and to some extent adjacent choroid plexus. A definite diagnosis relies on histological appearance of amyloid.

Methods We describe history, clinical presentation and laboratory findings that led to the diagnosis of multiple CNS amyloidomas in a male patient.

Results A 30-year-old male with unremarkable past medical history had a first episode of focal seizure affecting right arm which generalized subsequently. On examination the patient was alert without any focal deficits. MRI of his brain showed four high signal enhancing lesions without mass effect. Routine blood tests, HIV test, immunofixation of proteins and Computerized Tomography of his thorax and abdomen were normal. Cerebrospinal fluid examination showed near normal results. Stereotactic biopsy of the lesion in the left thalamus with Congo-red stain showed extensive deposits of amyloid as well as deposits in vessel walls. Extensive work-up for systemic amyloidosis was negative. Neuropsychiatric assessment disclosed no mental or cognitive abnormalities. His seizures were

controlled with valproate 1500mg/day and the patient recovered uneventfully. Because of the sites of the lesions surgery was not recommended.

Conclusion Although amyloidomas of the CNS are rare they must be considered in the differential diagnosis when atypical solitary or multiple lesions appear in brain or spine imaging producing relatively chronic non-specific symptoms.

P 2118

Cisplatin associated stroke in a patient with extragonadal seminoma

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We report a 43 old male patient who presented with acute thrombosis of the right brachial artery and ischemic stroke of right hemisphere after cisplatin infusion. Few reports in the literature describe cerebrovascular events after cisplatin infusion. However, the causal relation between a cisplatin and thrombotic events remains uncertain.

In our patient, a seminoma was diagnosed three month ago. One course of chemotherapy with cisplatin and etoposide was already applied without any severe side effects. The patient responded very well to chemotherapy. One day after the second course, the patient suffered from thrombosis of the right brachial artery and had multiple emboli in the right hemisphere. Neurological examination found severe neuropsychological deficits, as well as a left-sided hemiplegia. No cardiac source of embolism, or abnormal intravascular coagulation was found. The only predisposed risk factor for thrombosis was cigarette smoking. Because of good tumour response, further courses of cisplatin-based chemotherapy are planed. In order to prevent further thrombotic events, high dose heparin was given during the course of chemotherapy.

Cerebrovascular events related to cisplatin are rare, but have already been reported in patients with seminoma. Cisplatin is highly effective drug, also in patients with seminoma and therefore widely used. Although, no definite explanation for the association of cisplatin infusion and ischemic stroke can be proposed, a relation seems likely. Our report therefore emphasises a possible causal relation between chemotherapy and ischemic stroke in patients with seminoma. We recommend heparin in patients with thrombotic complications following cisplatin infusion.

P 2119

Clinical symptoms and prognostic factors in breast cancer-related meningeal metastases.

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Purpose Meningitis carcinomatosa (MC) is an uncommon but aggressive complication of advanced breast cancer with increasing incidence, recently.

Patients and methods We reviewed 20 cases of MC caused by breast cancer at our clinic. The neurological symptoms, pretreatment characteristics and the methods of MC treatment were analysed. The treatment consisted of intrathecal injection of 10 mg of methotrexate plus dexamethasone 4 mg, administered

weekly. 15 pts (75%) received systemic chemotherapy in parallel with intrathecal treatment and 2 pts (10%) – systemic hormonal treatment. The whole brain radiotherapy was performed additionally in fourteen (70%) pts.

Results The mean age at the time of diagnosis of MC was 45 years (range 29-70) and the median Karnofsky status was 50% (range 40-80%). The clinical symptoms at the time of diagnosis were headache (85%), nausea/vomiting (40%), confusion (30%), cerebellar signs (25%), paresis (25%) and pain in the thoraco-lumbar region (10%). Cancer cells in cerebrospinal fluid were detected in 100% of cases. Cerebrospinal fluid protein level was elevated in 70% of cases.

The mean of intrathecal treatment cycles was 6, (range 0-15 cycles).

The response was defined as clinical and laboratory improvement and was achieved in fourteen pts (70%). The median duration of survival was 112 days.

Conclusion Our observation suggests, how important prognostics factors in MC are: systemic chemotherapy, Karnofsky status at time the diagnosis of MC and the clinical response (reduction of headache and other symptoms) after the first 2–3 cycles of intrathecal infusion of methotrexate.

P 2120

Paraneoplastic neurologic syndrome – a case of lymphoma B

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Background Paraneoplastic neurological syndrome (PNS) is an unusual neurological disorder affecting patients with cancer. It's caused by complex non-metastatic, sometimes immune-mediated mechanisms and not by the tumour itself. We present a case of PNS that preceded the diagnosis of B-cell lymphoma.

Clinical case Female, 64-year-old, admitted 2 weeks before for paresis of IV cranial nerve, was readmitted with an insidious progressive distal and symmetrical sensory limb disturbance, anorexia and weight loss. On examination she had: IV cranial nerve paresis; impaired perception of vibration, pin and light touch with a stocking-and-glove distribution and absent tendon reflexes in lower limbs. Laboratory study showed slight pancitopenia, hepatic dysfunction, abnormal immunology and high CA-125. Liquor study was normal. Electromyography revealed focal mononeuropathies (essentially demyelinating) and the somatosensory-evoked potentials showed impairment of posterior columns. Pelvic imaging disclosed an ovarian cyst. An inflammatory aetiology was excluded and no systemic (including gynaecologic) tumour was found. Afterwards, she began painless jaundice, fever and dysphagia. Further study revealed severe pancitopenia and bone marrow biopsy showed lymphoma B. Quimiotherapy was initiated with clinical improvement.

Conclusion The PNS in this case was characterized by a cranial neuropathy and sensorimotor neuropathies that preceded a B-cell lymphoma. The clinical and laboratory findings (CA-125) misled our investigation towards a gynaecologic tumour when in fact it was primarily haematological. Nevertheless, the recognition of PNS is important because it may help avoiding unnecessary studies to determine the cause of neurological disturbances in cancer patients.