Question 20

A 68-year-old woman with stage III ovarian cancer presents with a progressive cerebellar syndrome. Cranial magnetic resonance imagine (MRI) demonstrates mild cerebellar atrophy and cerebrospinal fluid (CSF) examination reveals 10 lymphocytes/high power field, normal protein and glucose concentrations and negative cytology.

Which one of the following is the most appropriate next investigation
A. Anti-Purkinje cell antibodies (anti-Yo)
B. Repeat cerebrospinal fluid studies
C. Electroencephalogram (EEG)
D. Meningeal biopsy
E. Brain positron emission tomography (PET) scan

What are the investigations looking for?
A. Anti-Purkinje cell antibodies (anti-Yo)
   - The presence of anti-Yo antibodies in the serum of a woman with cerebellar symptoms is virtually conclusive evidence that she has paraneoplastic cerebellar degeneration and gynecologic, usually ovarian ca
B. Repeat cerebrospinal fluid studies
   - Low yield for example in paraneoplastic syndrome CSF reveals a mild pleocytosis (30-40 WC) slightly elevated protein (50-100mg) and elevated IgG
C. Electroencephalogram (EEG)
   - not very useful – looking for epileptic focus
D. Meningeal biopsy
   - suggesting meningeal mets – probably easier to rule out A first and/or add gadolinium to the MRI
E. Brain positron emission tomography (PET) scan
   - usually used for diagnosis of memory disorders and/or looking for brain tumour

Answer: A

Although rare – the presentation suggests a classic paraneoplastic syndrome. The only caveat is that a paraneoplastic syndrome such as a cerebellar syndrome usually presents before diagnosis as above so you wonder whether they are suggesting meningeal mets or other mets, but given there is an MRI already done a blood test seems more appropriate than PET
Antigens and antibodies provide the key for diagnosis CSF is usually non specific as mentioned

Paraneoplastic syndrome
- refers to symptoms or signs resulting from damage to organs or tissues that are remote from the site of a malignant neoplasm or its metastases.
- can affect most organs and tissues.
- common examples include cancer cachexia; hypercalcemia.; Cushing’s syndrome; Trousseau’s syndrome.
- Most occur because the tumor secretes substances that mimic normal hormones or that interfere with circulating proteins
- most or all paraneoplastic neurologic disorders are immune-mediated.
- The cancers causing paraneoplastic neurologic disorders are often asymptomatic and sometimes occult; it is the neurologic symptoms that take the patient to the doctor.
- The combination of an indolent tumor and severe neurologic disability suggests effective antitumor immunity coupled with autoimmune brain degeneration.

Types of syndromes
### Table 1. Paraneoplastic Syndromes of the Nervous System.

<table>
<thead>
<tr>
<th>Location of Syndrome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain and cranial nerves</td>
<td></td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>Gultekin et al.⁹</td>
</tr>
<tr>
<td>Brain-stem encephalitis</td>
<td>Barnett et al.⁷</td>
</tr>
<tr>
<td>Cerebellar degeneration</td>
<td>Peterson et al.⁸ Cao et al.⁹</td>
</tr>
<tr>
<td>Opsoclonus–myoclonus</td>
<td>Bataller et al.¹⁰</td>
</tr>
<tr>
<td>Visual syndromes</td>
<td></td>
</tr>
<tr>
<td>Cancer-associated retinopathy</td>
<td>Goldstein et al.¹¹</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Lieberman et al.¹²</td>
</tr>
<tr>
<td>Chorea</td>
<td>Croteau et al.¹³</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Golbe et al.¹⁴</td>
</tr>
<tr>
<td>Spinal cord</td>
<td></td>
</tr>
<tr>
<td>Necrotizing myelopathy</td>
<td>Rudnicki and Daimau¹⁵</td>
</tr>
<tr>
<td>Inflammatory myelitis</td>
<td>Babikian et al.¹⁶ Hedges et al.¹⁷</td>
</tr>
<tr>
<td>Motor neuron disease (amyotrophic lateral sclerosis)</td>
<td>Younger¹⁸</td>
</tr>
<tr>
<td>Subacute motor neuronopathy</td>
<td>Schold et al.¹⁹</td>
</tr>
<tr>
<td>Stiff-person syndrome</td>
<td>Brown and Marsden²⁰ Silverman²¹</td>
</tr>
<tr>
<td>Dorsal-root ganglia</td>
<td></td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>Graus et al.²²</td>
</tr>
<tr>
<td>Peripheral nerves</td>
<td>Rudnicki and Daimau¹⁵ Antoine et al.²³</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>Lee et al.²⁴</td>
</tr>
<tr>
<td>Acute sensorimotor neuropathy</td>
<td></td>
</tr>
<tr>
<td>Polyradiculoneuropathy (Guillain–Barré syndrome)</td>
<td>Lisak et al.²⁵</td>
</tr>
<tr>
<td>Brachial neuritis</td>
<td>Lachance et al.²⁸</td>
</tr>
<tr>
<td>Chronic sensorimotor neuropathy</td>
<td>Antoine et al.²⁵</td>
</tr>
<tr>
<td>Vasculitic neuropathy</td>
<td>Blumenthal et al.²⁷</td>
</tr>
<tr>
<td>Neuromyotonia</td>
<td>Lahmann et al.²⁸ Vincent²⁹</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td></td>
</tr>
<tr>
<td>Lambert–Eaton myasthenic syndrome</td>
<td>Carpentier and Delattre²⁰</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Vernino et al.³¹</td>
</tr>
<tr>
<td>Muscle</td>
<td></td>
</tr>
<tr>
<td>Polymyositis or dermatomyositis</td>
<td>Stockton et al.³²</td>
</tr>
<tr>
<td>Necrotizing myopathy</td>
<td>Levin et al.³³</td>
</tr>
<tr>
<td>Myotonia</td>
<td>Pascual et al.³⁴</td>
</tr>
</tbody>
</table>

Examples of specific antigens
Table 2. Antineuronal-Antibody–Associated Paraneoplastic Disorders. *

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Neuronal Reactivity</th>
<th>Protein Antigens</th>
<th>Cloned Genes</th>
<th>Tumor</th>
<th>Paraneoplastic Symptoms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Yo (PCA-1)</td>
<td>Cytoplasm, Purkinje cells</td>
<td>CDR3A, CDR3B</td>
<td>34 and 62 kD</td>
<td>Ovarian, breast, and lung cancers</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Peterson et al., Fatallah-Shaykh et al., Darnell et al.</td>
</tr>
<tr>
<td>Anti-Ri</td>
<td>Nucleus more than cytoplasm (central nervous system neurons)</td>
<td>Nova</td>
<td>53 and 80 kD</td>
<td>Breast, gynecologic, lung, and bladder cancers</td>
<td>Ataxia with or without opsoclonus–myoclonus</td>
<td>Jensen et al., Yang et al., Luque et al., Bucaknoorich et al.</td>
</tr>
<tr>
<td>Anti-Tr</td>
<td>Cytoplasm, Purkinje cells</td>
<td>?</td>
<td>23, 63, 145, and 205 kD</td>
<td>Hodgkin's lymphoma</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Pétula et al.</td>
</tr>
<tr>
<td>Anti-VGCC</td>
<td>Presynaptic neuromuscular junction</td>
<td>P/Q type VGCC, Mv18</td>
<td>64 kD</td>
<td>Small-cell lung cancer</td>
<td>Lambert–Eaton myasthenic syndrome</td>
<td>Carpentier and Delattre</td>
</tr>
<tr>
<td>Antiretal</td>
<td>Photoreceptors, ganglion cells</td>
<td>Recoverin</td>
<td>23, 63, 145, and 205 kD</td>
<td>Small-cell lung cancer, melanoma, gynecologic cancers</td>
<td>Cancer-associated retinopathy, melanoma-associated retinopathy</td>
<td>Maeda et al., Palans et al., Thirkill et al.</td>
</tr>
<tr>
<td>Anti-amphiphysin</td>
<td>Presynaptic nerve terminals</td>
<td>Amphiphysin</td>
<td>128 kD</td>
<td>Breast cancer, small-cell lung cancer</td>
<td>Stiff-person syndrome, paraneoplastic encephalomyelitis</td>
<td>Saiz et al., De Camilli et al., Foll et al.</td>
</tr>
<tr>
<td>Anti-CRMP5 (Anti-CV2)</td>
<td>Oligodendrocytes, neurons, cytoplasm</td>
<td>CRMP5 (POPs68)</td>
<td>66 kD</td>
<td>Small-cell lung cancer, thymoma</td>
<td>Encephalomyelitis, cerebellar degeneration, diabetes, sensory neuropathy</td>
<td>Yu et al.</td>
</tr>
<tr>
<td>Anti-PCA-2</td>
<td>Purkinje cytoplasm and other neurons</td>
<td>—</td>
<td>280 kD</td>
<td>Small-cell lung cancer</td>
<td>Encephalomyelitis, cerebellar degeneration, Lambert–Eaton myasthenic syndrome</td>
<td>Bataller et al.</td>
</tr>
<tr>
<td>Anti-Ma1</td>
<td>Neurons (subnucleus)</td>
<td>Ma2</td>
<td>40 kD</td>
<td>Lung cancer, other cancers</td>
<td>Brain-stem encephalitis, cerebellar degeneration</td>
<td>Rosenfeld et al.</td>
</tr>
<tr>
<td>Anti-Ma2</td>
<td>Neurons (subnucleus)</td>
<td>Ma2</td>
<td>45 kD</td>
<td>Testicular cancer</td>
<td>Limbic brain-stem encephalitis</td>
<td>Rosenfeld et al.</td>
</tr>
<tr>
<td>ANNA-1</td>
<td>Nuclei, Purkinje cells</td>
<td>—</td>
<td>170 kD</td>
<td>Lung cancer</td>
<td>Sensory neuropathy, encephalomyelitis</td>
<td>Chan et al.</td>
</tr>
<tr>
<td>Anti-mGluR1</td>
<td>Purkinje cells, olfactory neurons, hippocampus</td>
<td>Metabotropic glutamate receptor</td>
<td>—</td>
<td>Hodgkin's lymphoma</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Smitt et al.</td>
</tr>
<tr>
<td>Anti-VGCC</td>
<td>Peripheral nerve</td>
<td>VGKC</td>
<td>—</td>
<td>Potassium channels</td>
<td>Thymoma, small-cell lung cancer</td>
<td>Neurinmyotonia</td>
</tr>
<tr>
<td>Anti-MAG</td>
<td>Peripheral nerve</td>
<td>MAG</td>
<td>—</td>
<td>Wilderstrom's macroglobulinemia</td>
<td>Peripheral neuropathy</td>
<td>Vital</td>
</tr>
</tbody>
</table>

* There is no uniform nomenclature for some of the antibodies. In this article, we use the nomenclature developed in our laboratory. Where differences exist, they are indicated in parentheses. VGCC denotes voltage-gated calcium channel, VGKC voltage-gated potassium channel, and MAG myelin-associated glycoprotein.

Proposed pathogenesis
A tumor not involving the nervous system expresses a neuronal protein that the immune system recognizes as nonself. Apoptotic tumor cells are phagocytized by dendritic cells that migrate to lymph nodes, where they activate antigen-specific CD4+, CD8+, and B cells. The B cells mature into plasma cells that produce antibodies against the tumor antigen. The antibodies or the cytotoxic CD8+ T cells (or both) slow the growth of the tumor, but they also react with portions of the nervous system outside the blood–brain barrier. In the illustration, antibodies are reacting with voltage-gated calcium channels at the neuromuscular junction, causing the Lambert–Eaton myasthenic syndrome. In some instances, plasma cells and cytotoxic T cells cross the blood–brain barrier and attack neurons expressing the antigen they share with the tumor.

Treatment
Basis of treatment relates to the proposed pathogenesis of immune mediation – no established protocol, varying success which is usually based on whether or not neuronal death is a prominent feature of the disease

- removal of source of antigen by treatment of underlying tumour
- suppression of immune response
  - plasma exchange
  - intravenous immune globulin
  - corticosteroids
  - cyclophosphamide
  - tacrolimus
immunology

Tumor Immunity in Paraneoplastic Syndromes

The Tumor

Onconeural antigens are present in the tumor in all patients with antibody-positive paraneoplastic neurologic disorders and in many patients without such disorders. Moreover, the genes for these antigens are not mutated in tumor cells. Thus, paraneoplastic neurologic syndromes cannot be attributed to the infrequency of expression of the relevant tumor antigens or to mutations in the genes encoding these antigens.

The tumor is often occult, and the neurologic disorder typically precedes the diagnosis of the tumor. For example, patients with the Hu paraneoplastic syndrome typically harbor small-cell lung cancers that are limited to single nodules (53 of 55 patients in one study), despite the fact that most small-cell lung cancers (over 60 percent) are widely metastatic at diagnosis. In a few instances, unequivocal paraneoplastic syndromes may follow identification and even treatment of the tumor, and may sometimes herald a relapse.

The histologic features of tumors in paraneoplastic neurologic disorders do not differ from those of other tumors, except that the tumors may be heavily infiltrated with inflammatory cells. Many reports suggest that patients with paraneoplastic neurologic disorders have a better prognosis than patients with histologically identical tumors that are not associated with paraneoplastic neurologic disorders. The improved prognosis is not simply a result of earlier diagnosis of the cancer because the neurologic disease has led to a search for cancer. Patients with low titers of anti-Hu antibodies but without paraneoplastic disorders also have more limited small-cell lung cancer than patients who do not have the antibodies.

The Nervous System

The presence of antigen-specific cytotoxic T cells in paraneoplastic neurologic disorders was clearly documented after a patient with acute paraneoplastic cerebellar degeneration and anti-Yo antibodies was found to have activated T cells in her blood that were able to lyse target cells presenting the Yo (also called cdr2) antigen in vitro. Subsequent studies in chronically ill patients with paraneoplastic cerebellar degeneration have used autologous antigen-presenting cells (dendritic cells) to reactivate responses to the cdr2 antigen in memory cytotoxic T cells. Such reactivated responses have been elicited in all patients with paraneoplastic cerebellar degeneration whose T cells were tested for the phenomenon. These studies have been complemented by reports of a limited V[^3] chain T-cell repertoire in patients with the Hu syndrome (the V[^3] is one of the two chains, V[^3] and V[^α], of the T-cell receptor). Taken together, the evidence indicates that T-cell responses have an important role in paraneoplastic neurologic disorders.

Antibodies in paraneoplastic neurologic disorders react with the portion of the nervous system that is responsible for the clinical symptoms — for example, anti–Purkinje-cell antibodies occur in patients with paraneoplastic cerebellar degeneration. In many instances, the reaction is more widespread than the clinical findings. In paraneoplastic neurologic disorders affecting the brain, relatively high titers of the antibody in the cerebrospinal fluid (relative to total IgG) indicate that the antibody is synthesized within the brain, presumably by specific B cells that have crossed the blood–brain barrier.

One report described the presence of anti-Hu antibodies within neuronal nuclei of the central nervous system in patients who died of their paraneoplastic syndromes. Although some believe this finding to be an artifact, antibodies to double-stranded DNA, the hallmark of systemic lupus erythematosus, have been found within the nuclei of cells in patients with systemic lupus erythematosus.

Antibodies and Cytotoxic T Cells

The relative roles of humorally mediated immunity (antibodies) and cellular immunity (T cells) in paraneoplastic neurologic disorders are unresolved. This uncertainty is complicated by the fact that different paraneoplastic neurologic disorders may have different underlying mechanisms. When the target antigens are cell-surface receptors, as in the Lambert–Eaton myasthenic syndrome, myasthenia gravis, and a rare form of paraneoplastic cerebellar degeneration, antibodies appear to have the predominant role.

Paraneoplastic Cerebellar Degeneration

- Prodrome dizzyiness, oscillospsia, blurry or double vision, nausea and vomiting
- Develops into dysarthria, gait and limb ataxia with variable dysphagia
- MRI usually normal
- Extensive degeneration of Purkinje cells
- Immune-mediated pathogenesis
- Most frequent tumours involved: SCLC, cancer of breast and ovary and hodgkins lymphoma
Year 2003 Paper two: Questions supplied by Tricia

- Anti-yo antibodies in patients with breast and gynaecologic cancers and anti-Tr antibodies in patients with Hodgkin’s lymphoma antibodies typically associated with prominent pure cerebellar degeneration
- Antibodies to P/Q-type VGCC occur in some patients with SCLC and cerebellar dysfunction

Answer A

From the lectures

Ovarian Cancer - summary

Demographics
- 4% of all cancer and 5% of all cancer deaths
- One of the most common gynaecological malignancies
- 5th most frequent cause of cancer death in women
- Median age of diagnosis 63 years
- Since 1970s little change in incidence and death rates
- Yearly mortality approx 65% of the incidence rate
- Long-term follow-up of suboptimally debulked stage II and stag IV patients reveal a 5-year survival rate of less than 10% even with platinum-based combination therapy

Genetics
- 5-10% familial
- 3 patterns ovarian alone | ovarian and breast ca | ovarian and colon ca
- Most important risk factor is family history of 1st relative with disease
- Highest risk women with 2 or more 1st degree relatives with ovarian ca
- BRCA1&2 (see P2q2)

Natural history / screening
- Nat history poorly understood
- Entire peritoneum at risk – peritoneal carcinomatosis may develop after oophorectomy
- The syndrome of extra-ovarian peritoneal carcinomatosis is characterised by widespread intra-peritoneal epithelial carcinoma in the presence of histological normal ovaries
- No evidence premalignant lesion eg cyst
- No available screening
- Diagnosis via laparotomy

Tumour behaviour
- Incidence of positive nodes at primary surgery
  - 24% stage I
  - 50% stage II
  - 74% stage III
  - 73% stage IV
- Tumour cells block lymphatics leading to ascites
- Transdiaphragmatic spread to pleura common
- Diagnosis usually at later stage as early stage disease often assymptomatic
Prognostic Features

- FIGO stage (federation of internationale de Gynecologie et d'Obstetrique)
- Histologic subtype (mucinsous and clear cell worse)
- Histologic grade
- Age – older worse
- Performance status
- Disease volume prior to any surgical debulking
- Malignant ascites or positive peritoneal washings
- Ruptured capsule
- Dense ovarian adhesions
- Residual tumour following primary cyto-reductive surgery
- CA125 has a high correlation with survival when measured one month after the third course of chemotherapy for patients with stage III or stage IV disease

Cellular classifications

- Serous cystadenocarcinomas
- Mucinous cystadenocarcinomas
- Endometrioid adenocarcinomas
- Clear cell cystadenocarcinomas
- Unclassified tumours

Treatment

Stage I – low risk

- Surgery abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy
- Unilateral salpingo-oophorectomy can be considered (childbearing)

Stage I high risk stage II

- Surgery
- Chemo / radiotherapy
- There is a survival advantage for all subgroups of patients with early stage ovarian cancer treated after surgery with platinum-based chemotherapy

Stage III

- Surgery radical debulking
- Systemic chemo: paclitaxel and platinum
- No survival advantage for second look laparotomy
- Intra-peritoneal chemo – 8 month survival advantage in some patients

Stage IV

- Evidence por
- IV paclitaxel plus IV cisplatin or IV carboplatin commonly used