MOVEMENT DISORDERS IN PARANEOPlastic DISORDERS

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DISCLOSURES

• Dr Francesca Morgante has received honoraria as a Consultant & Advisory Boards from Medtronic, Merz and Chiesi. She has received honoraria for speaking from Merz, Bial, Medtronic, Chiesi, Abbvie, Zambon.

• She serves in the Editorial board of Movement Disorders, Movement Disorders Clinical Practice and European Journal of Neurology.

• No disclosures related to this talk.
PARANEOPLASTIC NEUROLOGIC SYNDROMES (PaNS): General concepts

- PaNS are complications of cancer that cannot be attributed to direct effects of the neoplasm or its metastases.
- PaNS include an extensive group of immune-mediated disorders that can affect any part of the central or peripheral nervous system.
- More commonly tumors associated with PaNS:
  - Small-cell lung cancer (SCLC)
  - Ovarian cancer
  - Breast cancer
  - Neuroendocrine tumors
  - Thymoma
  - Lymphoma
- PaNS more commonly develop prior to the cancer diagnosis.
- PaNS may occur with may in association with \textit{onconeuronal} or \textit{antineuronal cell surface} antibodies.
PARANEOPLASTIC NEUROLOGIC SYNDROMES (PaNS): General concepts

- Only 60% of PaNS of CNS and less than 20% of those affecting the peripheral nervous system are associated with antineuronal (or antineuromuscular) antibodies.
- Antibodies can rarely be found at low titers in some patients with cancer without PaNS, and for some antibodies, testing method and whether serum or CSF was used increase the risk of false negative or positive results.
- The diagnosis of PaNS be based on clinical criteria with antibody test results used as confirmatory but not exclusionary evidence of PaNS.
- The same antibody can produce different clinical syndromes. For example: anti-Antiamphiphysin is associated to Stiff-person syndrome, encephalomyelitis, paraneoplastic cerebellar degeneration.
- For syndromes in which the antigenic targets are intracellular (e.g., Hu, Yo, among others), T-cell mechanisms appear to produce irreversible neuronal destruction that occurs early and rapidly. Poor prognosis.
- For syndromes with antineuronal cell surface antibodies, treatment of the tumour along with removal of the antibodies or immunosuppression can be highly effective. The recovery process can be slow and occurs over months (i.e. anti NMDA-R encephalitis)

Hoftberger et al, Curr Op Oncol. 2015
Dalmau and Rosenfeld, 2020
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 is the investigation of first choice followed by CT.

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.

Titulaer et al, 2011
PaNS CLINICAL MANIFESTATIONS

- Encephalomyelitis: multifocal involvement with CNS (+/- MDS) and Peripheral NS involvement
- Limbic encephalitis

- Paraneoplastic cerebellar degeneration
- Opsoclonus–myoclonus
- Peripheral Nerve Hyperexcitability (Neuromyotonia)
- Stiff Person Syndrome and PERM
- Paraneoplastic Chorea

- Brainstem encephalitis

- Paraneoplastic Syndromes of the Visual System: retinitis, uveitis
- Paraneoplastic Enteric neuropathy
- Paraneoplastic syndromes of the peripheral nervous system
- Paraneoplastic syndromes of the neuromuscular junction
- Paraneoplastic myopathic syndromes
PARANEOPLASTIC CEREBELLAR DEGENERATION
PARANEOPLASTIC CEREBELLAR DEGENERATION (PCD)

Subacute onset of truncal and limb ataxia, dysarthria, and nystagmus.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Neurologic syndrome</th>
<th>Common cancer association</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onconeural antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Yo (PCA-1)</td>
<td>PCD</td>
<td>Ovary, breast</td>
<td>Poor response to treatment</td>
</tr>
<tr>
<td>Anti-Ri (ANNA-2)</td>
<td>PCD, opsoclonus</td>
<td>Gynecologic, breast</td>
<td>Poor response to treatment</td>
</tr>
<tr>
<td>Anti-Tr/DNER</td>
<td>PCD</td>
<td>Hodgkin’s lymphoma</td>
<td>80% of patients are men &lt;45 years</td>
</tr>
</tbody>
</table>

| Neuronal cell surface antibodies | | |
| Anti-VGCC | LEMS, PCD | SCCLC | Responds well to treatment |
| Anti-GluR1 | PCD | Hodgkin lymphoma | Only a few cases; some improved |

60% of cases

Diffuse loss of Purkinje cells

Inflammatory CFS:

- ↑ white cell count
- ↑ proteins
- Intrathecal synthesis of IgG

Initial MRI often normal. Cerebellar atrophy only with substantial latency

Other Ab reported associated to PCD: anti-Zic4 (isolated ataxia), anti-PCA2, anti-ANNA3, anti-SOx1 (often combined with other PNS syndromes)
PCD: PROGRESSION AND SURVIVAL

- Associated mainly with **Small-cell lung cancer, breast and ovarian cancer, Hodgkin’s lymphoma.**
- Subacute onset and rapid progression of ataxia (severe ataxia in <12 weeks)
- In most cases, ataxia precedes the detection of the underlying tumor.

Revised search for the primary tumor is required

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gynecologic (n = 18)</th>
<th>Breast (n = 12)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal relation between PCD and tumor diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCD &gt; 3 mo before tumor diagnosis</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Simultaneous</td>
<td>8</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>PCD &gt; 3 mo after tumor diagnosis</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Staging at tumor diagnosis†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Regional (lymph nodes or adjacent structures)</td>
<td>7</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Systemic metastases</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>No tumor</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>13</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Response to tumor treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Other response</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>No treatment</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Median survival, mo</td>
<td>15</td>
<td>100</td>
<td>22</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncologic</td>
<td>9</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Neurologic</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*Rojas et al, Neurology 2000*
### Table 1. Characteristics of 9 Patients With Antineuronal Nuclear Autoantibody Type 2 (ANNA-2, Also Known As Anti-Ri)–Associated Jaw Dystonia or Laryngospasm

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>ANNA-2 Titers</th>
<th>Location of Carcinoma</th>
<th>Opsonous</th>
<th>Jaw Dystonia</th>
<th>Laryngospasm</th>
<th>Other Neurologic Findings</th>
<th>Magnetic Resonance Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5768</td>
<td>560</td>
<td>Breast</td>
<td>No</td>
<td>Yes, mouth could open only partially, 1st finger’s breadth at peak attack</td>
<td>Possible</td>
<td>Ataxia, dysphagia, postural instability, axial and neck rigidity, horizontal gaze paresis, bilateral ptosis, subtle myoclonus, and diplopia</td>
<td>Normal</td>
</tr>
<tr>
<td>2.8758</td>
<td>7580</td>
<td>Breast</td>
<td>No</td>
<td>Yes, could open mouth only partially; recurrent tongue biting</td>
<td>Yes, episodic; with occasional respiratory distress; required tracheotomy</td>
<td>Ataxia, dysphagia, postural instability, axial and neck rigidity or dystonia, horizontal gaze paresis, subacute myoclonus, tremor, and loss of small and fine f</td>
<td>Normal</td>
</tr>
<tr>
<td>3.4144</td>
<td>12280</td>
<td>Breast</td>
<td>Possible</td>
<td>Yes, difficulty opening mouth; recurrent jaw spasms; tongue biting; and lost 22.7 kg</td>
<td>Yes, episodic; once caused loss of consciousness; subsequent fatal episode</td>
<td>Ataxia, generalized rigidity, horizontal gaze paresis, oscillopsia, leg spasms, tinnitus, and incontinence</td>
<td>Normal</td>
</tr>
<tr>
<td>4.1280</td>
<td>7580</td>
<td>Breast</td>
<td>Yes, transient</td>
<td>Yes, inability to open mouth; lost 9 kg</td>
<td>No</td>
<td>Ataxia, horizontal gaze paresis, oculopalatal myoclonus, rigidity of the lower extremity, and spasticity</td>
<td>Unavailable</td>
</tr>
<tr>
<td>5.7720</td>
<td>3840</td>
<td>Cervix</td>
<td>No</td>
<td>Yes, acute, requiring intubation</td>
<td>Yes, episodic</td>
<td>Ataxia, rigidity, vertigo, dysphagia, and quadriplegia</td>
<td>Gadolinium enhancement in mesial temporal lobes, uncus, hemispheric white matter, and pons (by radiology report)</td>
</tr>
<tr>
<td>6.8160</td>
<td>30720</td>
<td>Breast</td>
<td>Yes</td>
<td>Yes, mouth could open only partially; jaw spasms; tongue biting</td>
<td>No</td>
<td>Ataxia, dysphagia, generalized rigidity, hyperreflexia, bilateral Babinski signs, clonus, difficulty opening eyes, horizontal gaze paresis, tremor, and neck dystonia</td>
<td>Normal</td>
</tr>
<tr>
<td>7.8660</td>
<td>245760</td>
<td>Lung, non-small cell</td>
<td>Yes</td>
<td>No</td>
<td>Yes, episodic</td>
<td>Ataxia, nystagmus, myoclonus</td>
<td>Normal</td>
</tr>
<tr>
<td>8.7250</td>
<td>15360</td>
<td>Breast</td>
<td>No</td>
<td>Possible</td>
<td>Yes, episodic; required ICU admission (3 times); tracheotomy considered</td>
<td>Ataxia, dystonia, dizziness, deep venous thrombosis, left upper limb weakness, and dysphagia</td>
<td>Transient nonenhancing T2-weighted signal in right insular cortex</td>
</tr>
<tr>
<td>9.4720</td>
<td>15360</td>
<td>Breast</td>
<td>No</td>
<td>Yes, jaw clenching (6 times per hour); tongue biting; tinnitus; required gastrojejunal feeding tube</td>
<td>Not documented but required tracheotomy at ICU admission with respiratory failure</td>
<td>Ataxia, nystagmus, myoclonus</td>
<td>Increased T2-weighted and FLAIR signal in dorsal pons</td>
</tr>
</tbody>
</table>

Axial rigidity and postural instability.
PCD: TREATMENT

• Treat the underlying tumor and start immunomodulatory drugs (plasma exchange, PLEX; i.v. IG, Steroids) (*Vitaliani et al. 2008*)

• Only rare cases respond to PE, i.v. IG, Steroids: need for early diagnosis.

• Cyclophosphamide, tacrolimus, rituximab, or mycophenolate: in patients who fail to stabilize or improve on less aggressive therapies (*Greenlee JE, Curr Treat Options Neurol. 2013*)

• Better outcome in PCD associated with anti-Tr and anti-mGluR1 antibodies in Hodgkin’s disease: might improve with therapy (*Bernal et al, Neurology 2003*)
Main clinical syndrome: Vertigo, ataxia, and diplopia

Associated tumour: Seminoma

The onset of the neurologic syndrome preceded the diagnosis of seminoma in 9 of the 13 patients
OPSOCLONUS MYOCCLONUS SYNDROME (OMS)

- **Opsoclonus**: arrhythmic, large-amplitude conjugate saccades occurring in all directions of gaze without a saccadic interval
- **Myoclonus** of the head, trunk, or extremities
- Severe **Ataxia**
- **Neuropsychological abnormalities** in many patients

Armangue et al., 2014
Armangue et al., 2016

Neuroblastoma

SCLC

Ohara S et al, MDJ 2007
OPSOCOLONUS MYOCLONUS SYNDROME (OMS): Causes and Antibodies

- Paraneoplastic or idiopathic (both immunomediated)
- Neuroblastoma: children
- SCLC
- Non–small cell lung cancer (NSCLC)
- Breast
- Bladder
- Thyroid
- Hodgkin disease
- Ovarian Teratoma: without identifiable antibodies

Abs associated to adult paraneoplastic OMS

- Anti-GlyR: lung cancer and OMS
- Anti-HNK-1: lung cancer and OMS
- Anti-Ri: breast cancer and OMS
- Anti-Ma2
- Anti-Zic4
- Anti-Hu
- Anti-Yo
- Anti-CV2/CRMP5
- Anti-VGCC

Only 11% in this cohort had antibodies associated to OMS

Armangue’ et al, Jama Neurology 2016
PARANEOPLASTIC ENCEPHALITIS WITH HYPERKINETIC MDS

- Anti-NMDA-R

- Anti-LG1
- Anti-CASPR2: Neuromyotonia +/- CNS involvement (Morvan Syndrome)

- Anti-GABA-A-R: Limbic encephalitis with severe seizures (also associated with rapid onset of dystonia)
Anti-NMDA-R encephalitis

- The most common of the encephalitis associated with antibodies to cell surface antigens.
- Onset: behavioural changes, memory deficits, and psychosis

Two types of triggers:
- Herpes simplex encephalitis
- Tumors
  - Females >12 and <45 years: ovarian teratoma
  - Females/males >45 years: rare association with solid tumors

*Dalmau et al, Lancet Neurology 2019*
Anti-NMDA-R encephalitis:
Complex hyperkinetic MDS

N= 34 with NMDAR-AbE

Co-occurrence of stereotypies, chorea and dystonia
Low interrater agreement for dystonia, chorea or stereotypies

Varley et al, JNNP 2019
From Varley et al, JNNP 2019

From Baizabal-Carvallo et al, MDJ 2013

chorea

repetitive orofacial stereotypies, dystonic contractions of the left side of face, blepharospasm, chorea

1- to 2-Hz lower limb myorhythmia
**Anti-NMDA-RabE: Diagnosis**

**Inflammatory CFS:**
- ↑ white cell count
- ↑ proteins
- intrathecal synthesis of IgG

**Search NMDA-R Ab in CFS and Seerum**

**Hyppocampal lesions associated with poorer outcome and relapse**

**Varley et al, JNNP 2019**

**Zhang et al, AJNR 2018**

Type 1: normal
Type 2: lesions in the hippocampus.
Type 3: multifocal lesions involving frontal cortex, BG, cerebellum and brainstem. No hippocampal lesions
Type 4: multifocal lesions involving frontal cortex, BG, cerebellum and brainstem + hippocampal lesion
Seven of 23 patients (30.4%) had a unique electrographic pattern, which we named “extreme delta brush” because of its resemblance to waveforms seen in premature infants.

Generalized rhythmic and semirhythmic delta frequency activity at 1 Hz with superimposed, frontally predominant bursts of rhythmic beta frequency activity.
Anti-LGI1 and CASPR2

Stop testing for autoantibodies to the VGKC-complex: only request LGI1 and CASPR2

Sophia Michael,1,2 Patrick Waters 1, Sarosh R Irani 1,2

Pathogenic antibodies

- LGI1-antibody
- CASPR2-antibody
- FBDS
- NMT
- Extracellular antibodies
- Intracellular antibodies
- Limbic encephalitis
- Dysautonomia
- NMT

Autoantibody

<table>
<thead>
<tr>
<th>Evidence</th>
<th>LGI1</th>
<th>CASPR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
<td>Well-delineated clinical syndromes?</td>
<td>Yes24,25;</td>
</tr>
<tr>
<td></td>
<td>Faciobrachial dystonic seizures; Limbic encephalitis (other frequent focal seizure semiologies, encephalopathy, sleep disorder, amnesia, anxiety, emotionality dysautonomia); Hyponatraemia in ~65%</td>
<td>CNS: limbic encephalitis—seizures, confusion, hallucinations, insomnia</td>
</tr>
<tr>
<td></td>
<td>More rarely, neuromyotonia and Morvan’s syndrome</td>
<td>Morvan’s syndrome: above including insomnia and dysautonomia, often with weight loss</td>
</tr>
<tr>
<td>Demographics: gender ratio and median age of onset</td>
<td>M (2:1) 60–70 years25</td>
<td>M (8:1) 50–60 years</td>
</tr>
<tr>
<td>Immunotherapy-responsive (%)</td>
<td>Highly: 100%26 96%24 97%25 29 78%9</td>
<td>Highly: 100%37 86%26</td>
</tr>
<tr>
<td>Serological Epitope</td>
<td>Extracellular (both receptor docking and non-docking domains of this secreted protein)8,9,28</td>
<td>Extracellular domain8,9,28</td>
</tr>
<tr>
<td>Rate in healthy controls</td>
<td>&lt;1%38</td>
<td>&lt;1%38</td>
</tr>
<tr>
<td>Other associations/markers</td>
<td>Rarely thymoma &lt;5%</td>
<td>Thymoma 20-50%, especially those with Morvan’s syndrome and neuromyotonia</td>
</tr>
</tbody>
</table>

Anti-LGI1 disease: FBDS, amnesia, confusion and executive dysfunction, often with hyponatraemia. FNBS duration: seconds. Ictal epileptiform EEG

FBDS show striking time-sensitive responses to immunotherapy, and their cessation can prevent the development of cognitive impairment.

LGI1+ with Cognitive impairment: Medial Temporal lobe high-signal on T2 MRI
**Anti-CASPR2 - Phenomenological Hallmarks**

Peripheral Nerve Hyperexcitability (PNH) = Neuromyotonia

Morvan Syndrome = Neuromyotonia, myokymia, severe insomnia, hyperhidrosis, and encephalopathy causing confusion, hallucinations, and fluctuating cognition

Video from Vale et al, The Lancet 2017
NEUROMYOTONIA

Disorder of generalised peripheral nerve hyperexcitability (PNH), manifesting as spontaneous, continuous muscle activity of peripheral nerve origin.

Clinical Features:
- muscle twitching at rest (visible myokymia)
- cramps, which can be triggered by voluntary or induced muscle contraction
- impaired muscle relaxation, or pseudomyotonia

Isaacs, 1961; Newsom-Davis and Mills, 1993

Neuromyotonic discharges

- Spontaneous, continuous, irregularly occurring doublet, triplet or multiplet single motor unit (or partial motor unit) discharges, firing at a high intraburst frequency (30–300 Hz).
- After discharges at Nerve conduction studies

Spontaneous discharges at the highest frequencies (150–300 Hz) firing in prolonged bursts that begin, ending abruptly, and often wane in amplitude

Maddison, Clinical Neurophysiology 2006
• Most commonly associated condition = myasthenia gravis
• Thymoma in 21.8%
• Non-thymoma malignancies uncommon: 10.6%

**Inflammatory CFS (30%):**
- ↑ white cell count
- ↑ proteins

**Brain MRI**
- Normal in 53%
- T2 hyperintensities in the medial temporal lobes, or hippocampal atrophy, mesial temporal sclerosis, or hippocampal sclerosis
Stiff person syndrome (SPS) is an unusual disorder characterized by progressive muscle stiffness, aching, spasms, and rigidity. Hyperekplexia might be a feature (pronounced startle responses to tactile or acoustic stimuli).

**PARANEOPLASTIC STIFF PERSON SYNDROME**

Non-paraneoplastic SPS associated to anti GAD antibodies

**Paraneoplastic SPS antibodies:**
- **Anti-Amphiphysin**: Breast cancer, small cell lung cancer. Association with sensory neuronopathy and mielopathy

- **Anti-Glycine receptors (anti-GlyR)**: In 9%: thymoma, SCLC, breast cancer, Hodgkin lymphoma, chronic lymphocytic leukaemia
- **DPPX**: In 7% B-cell neoplasms
**PROGRESSIVE ENCEPHALOMYELITIS WITH RIGIDITY AND MYOCLONUS ASSOCIATED TO ANTI-GLY-R ANTIBODIES**

PERM is a rare disorder of subacute onset presenting as limb and truncal rigidity, muscle spasms, brainstem signs, and hyperekplexia.


### Clinical features

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Clinical features at onset n (%)</th>
<th>Clinical features at peak n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>45</td>
<td>30</td>
</tr>
<tr>
<td>Spasms/stiffness/rigidity/myoclonus (neck, trunk or limb muscles)</td>
<td>31 (69%)</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>Oculomotor disturbance: nerve or gaze palsy (eyelid ptosis, diplopia, nystagmus, slow/jerky movements)</td>
<td>18 (40%)</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Trigeminal, facial and bulbar disturbance (dysphagia, dysarthria, difficulty chewing, facial numbness, trismus)</td>
<td>21 (47%)</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>Excessive startle (spontaneous or triggered by noise or touch)</td>
<td>19 (42%)</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>Walking difficulties/falls, mostly related to stiffness/rigidity/spasms</td>
<td>19 (42%)</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>Limb paresis/pyramidal signs</td>
<td>10 (22%)</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>Limb or gait cerebellar ataxia</td>
<td>6 (13%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Autonomic disturbance (hyper/hypo/hydrosis, dry mouth, brady/tachycardia, hypo/hypertension, bladder, bowel or sexual dysfunction)</td>
<td>13 (29%)</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Cognitive impairment/encephalopathy/seizures</td>
<td>16 (36%)</td>
<td>15 (50%)</td>
</tr>
<tr>
<td>Sensory symptoms/pain</td>
<td>10 (22%)</td>
<td>14 (47%)</td>
</tr>
<tr>
<td>Respiratory failure (admission in ICU/ventilation)</td>
<td>8 (18%)</td>
<td>8 (27%)</td>
</tr>
</tbody>
</table>

### Tumours in past medical history and successfully treated

- 5 (n = 1 breast cancer; n = 1 breast cancer and thymoma; n = 1 thymoma and lymphoma; n = 1 Hodgkin lymphoma; n = 1 malignant melanoma; n = 3 thymoma; n = 1 bladder cancer associated with monoclonal gamopathy IgM (10%); n = 1 metastases from previous treated breast cancer)

### Tumours identified during the current neurological illness

- 4 (n = 1 breast cancer; n = 1 breast cancer and thymoma; n = 1 thymoma and lymphoma; n = 1 Hodgkin lymphoma; n = 1 malignant melanoma; n = 3 thymoma; n = 1 bladder cancer associated with monoclonal gamopathy IgM (10%); n = 1 metastases from previous treated breast cancer)
• Non-Hodgkin Lymphoma one year before.
• Subacute onset of painful spasms in lower limbs. No brainstem features.
• Anti-GlyR antibodies lower limbs stiffness with prominent pyramidal features.
• Serum and CFS anti-GlyR Ab ++

After PLEX, i.v. and oral steroids. Currently treated with rituximab

Courtesy of Dr V. Oppo and Dr G. Cossu
### PARANEOPLASTIC CHOREA ASSOCIATED WITH CRMP-5 ANTIBODY

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>Movement Disorder</th>
<th>Other Paraneoplastic Neurological Manifestations</th>
<th>Other Neuronal Autoantibodies</th>
<th>Treatment/Chorea Response</th>
<th>Survival after Onset (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69/M</td>
<td>Right hemichorea and dystonia, hyperkinetic dystasia</td>
<td>SCLC</td>
<td>129k serum</td>
<td>IVM/Improved</td>
<td>2, dead</td>
</tr>
<tr>
<td>2</td>
<td>64/F</td>
<td>Generalized chorea, most prominent on right, hyperkinetic dystasia</td>
<td>SCLC</td>
<td>129k serum</td>
<td>Chemotherapy and IVIG/Improved</td>
<td>17, alive</td>
</tr>
<tr>
<td>3</td>
<td>80/F</td>
<td>Choreo of face and limbs, prominent in left leg</td>
<td>Anoxia/angiitis, cognitive dysfunction</td>
<td>VGCN N 83pM, ANNA-1 15,360</td>
<td>Chemotherapy</td>
<td>37, alive</td>
</tr>
<tr>
<td>4</td>
<td>66/M</td>
<td>Choreoathesia of face and limbs</td>
<td>Limbic encephalitis, myelitis</td>
<td>SCLC and Lung ACA</td>
<td>Chemotherapy</td>
<td>24, dead</td>
</tr>
<tr>
<td>5</td>
<td>68/M</td>
<td>Generalized chorea, hyperkinetic dystasia</td>
<td>Limbic encephalitis, myelitis</td>
<td>SCLC</td>
<td>Chemotherapy</td>
<td>13, alive</td>
</tr>
<tr>
<td>6</td>
<td>66/M</td>
<td>Choreo of mouth, tongue, and limbs, hyperkinetic dystasia</td>
<td>Sensory neuropathy</td>
<td>VGCN N 157pM, ANNA-1 4,648</td>
<td>Chemotherapy</td>
<td>22, dead</td>
</tr>
<tr>
<td>7</td>
<td>67/F</td>
<td>Choreoathesia of face and limbs</td>
<td>Limbic encephalitis, visual loss, anosmia/agnosia</td>
<td>SCLC</td>
<td>Chemotherapy/Improved</td>
<td>38, alive</td>
</tr>
<tr>
<td>8</td>
<td>66/F</td>
<td>Generalized chorea, hallucinosis, hyperkinetic dystasia</td>
<td>Limbic encephalitis</td>
<td>Lung mass</td>
<td>Chlorpromazine/Improved</td>
<td>14, alive</td>
</tr>
<tr>
<td>9</td>
<td>72/F</td>
<td>Choreoathesia of face dystasia of left face, hyperkinetic dystasia</td>
<td>Limbic encephalitis</td>
<td>ANNA-1 960</td>
<td>Chemotherapy/Improved</td>
<td>27, alive</td>
</tr>
<tr>
<td>10</td>
<td>73/M</td>
<td>Choreo of arms and trunk, ataxia, dystasia</td>
<td>Limbic encephalitis, visual loss, ataxia, gait ataxia</td>
<td>SCLC</td>
<td>Chemotherapy</td>
<td>22, dead</td>
</tr>
<tr>
<td>11</td>
<td>75/F</td>
<td>Choreoathesia of face and neck</td>
<td>Limbic encephalitis</td>
<td>Renal cell</td>
<td>IVM/Improved</td>
<td>42, alive</td>
</tr>
<tr>
<td>12</td>
<td>71/F</td>
<td>Generalized chorea, hyperkinetic dystasia, ataxia, anosmia/agnosia</td>
<td>Limbic encephalitis</td>
<td>SCLC</td>
<td>Chemotherapy/No benefit</td>
<td>10, alive</td>
</tr>
<tr>
<td>13</td>
<td>71/M</td>
<td>Choreo of hands and face</td>
<td>Limbic encephalitis, visual loss</td>
<td>Lung mass</td>
<td>IVGKC 359pM</td>
<td>12, dead</td>
</tr>
<tr>
<td>14</td>
<td>74/F</td>
<td>Left hemiballismo and facial gazing</td>
<td>Limbic encephalitis, visual loss</td>
<td>SCLC and Lung ACA</td>
<td>Chemotherapy</td>
<td>4, alive</td>
</tr>
<tr>
<td>15</td>
<td>65/F</td>
<td>Choreo of face and limbs, hyperkinetic dystasia</td>
<td>Limbic encephalitis, visual loss, ataxia, gait ataxia</td>
<td>VGCN N 62pM</td>
<td>Chemotherapy</td>
<td>6, dead</td>
</tr>
</tbody>
</table>

- Often associated to SCLC
- Often combined with cognitive impairment, optic neuritis, myelitis
- CRMP-5 Ab also associated to paraneoplastic Parkinsonism (Yap et al, MDCP 2016)

*Video from Vaswani et al, MDCP 2020*

Vernino et al, Annals neurology 2002
Two of the 7 patients developed hyperkinetic movement disorders during treatment with immune checkpoint inhibitors (nivolumab and pembrolizumab),

A similar phenotype (generalized hyperkinetic movement disorder and bilateral striatal lesions on MRI) in children with PDE10A mutations parallels this autoimmune phenotype (Diggle et al, 2016; Miyatake et al, 2018)
PARANEOPlastic NeuROLOGIC SYNDROMES: DIAGNOSTIC APPROACH

Presentation with Classic PaNS (i.e. OMS, PCD)

Onconeural Ab and neuronal surface Ab search

Careful review of associated medical condition and neurological manifestations

EEG
EMG/NCS

Correlate clinical syndrome with Ab and Tumour found

Correlate clinical syndrome with Ab and Tumour found

Onconeural Ab and neuronal surface Ab search

Brain MRI
CFS Analysis

CT CAP
Mammography
Testicular US
Pelvic US
Skin exam

Exclude rapidly progressive neurological syndromes with MDS (i.e. CJD, infectious, metabolic, vascular)

START IMMUNOTHERAPY
- PLEX
- I.V. IG
- I.V. STEROIDS
- Rituximab
- Ciclophosphamide

The diagnosis of a paraneoplastic neurologic syndrome should not await the results of antibody testing that may be delayed by days or weeks (and for some syndromes can be negative).

If primary screening is negative, repeat screening after 3–6 months and screen every 6 months up till 4 years.
ACKNOWLEDGEMENTS

ST. GEORGE’S MDS TEAM

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- **Neurosurgeon:** Erlick Pereira
- **Neuropsychologist:** Priyanka Pradhan
- **PD nurses:** Alison Leake, Catherine Parry, Lucy Kerogoi