5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 9

Antibodies: From autoimmune encephalitis to paraneoplastic myelopathies (Level 2)

Paraneoplastic and Autoimmune Myelopathies

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Paraneoplastic and Autoimmune Myelopathies

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Disclosures

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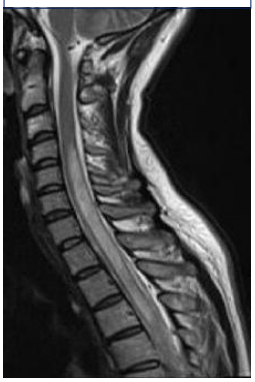
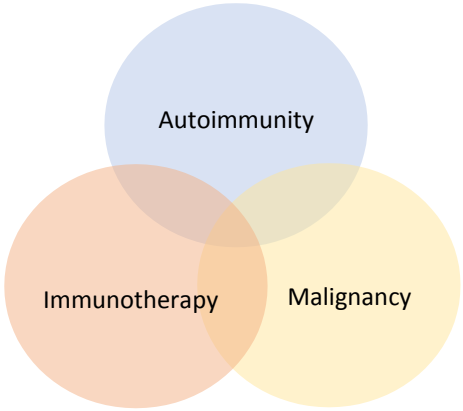
- Speaker Honoraria or Travel grants: Biogen Idec, Novartis, and the Guthy-Jackson Charitable Foundation.

Myelopathy Myelitis





Complex field

Better imaging techniques
Autoantibody discovery
New drug development

⬇

Old clinical pictures/syndromes:
Reclassified
Better understood
Better treated

MOG-Ab: Myelitis

PN, 40yo M

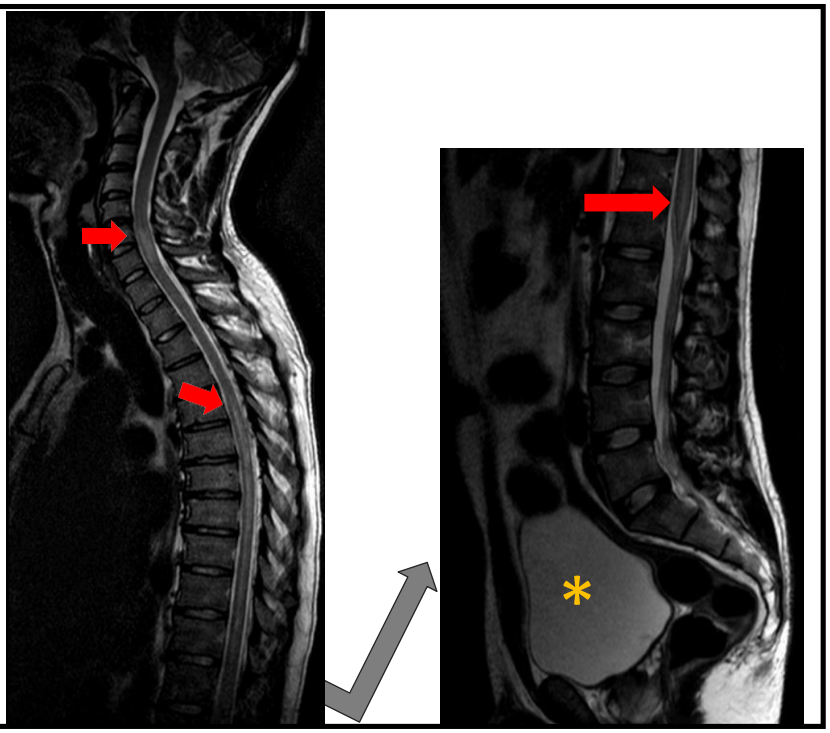
PMH: No previous illnesses; no medications
SH: RAF engineer
FH: None

PRESENTATION
- **Acute** - Tingling sensation in the legs and trunk. - **Urinary retention requiring catheterisation**. - Mild leg weakness - unaided

Investigations

Blood: MOG-Ab positive
CSF: WCC 2; glucose normal; protein 0.75 g/L

*MRI: LETM, involving the **conus***



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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES
- **Acute** - Tingling sensation in the legs and trunk. - **Urinary retention requiring catheterisation**. - Mild leg weakness - unaided	- Treated with 5 days of IVMP. - Back to full power in the limbs and normal sensation within 5 days post treatment completion. - Improved bladder and erectile dysfunction slowly

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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES	LONG TERM TREATMENT AND OUTCOMES
- **Acute** - Tingling sensation in the legs and trunk. - **Urinary retention requiring catheterisation**. - Mild leg weakness - unaided	- Treated with 5 days of IVMP. - Back to full power in the limbs and normal sensation within 5 days post treatment completion. - Improved bladder and erectile dysfunction slowly	- After acute treatment he was maintained on low reducing dose oral steroids for 9 months. - **Bladder and erectile dysfunction resolved in 6 months** - Remained relapse free.

MOG-Ab myelitis (ADEM-like)

JS, 25yo M

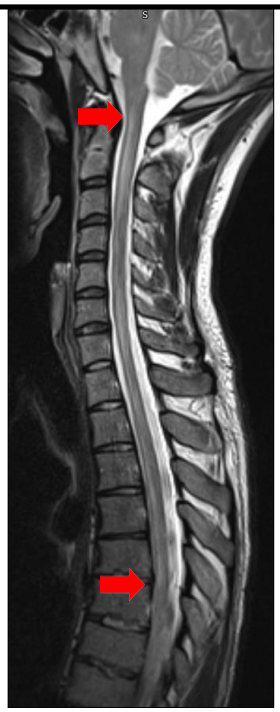
PMH: None; no previous neurological illness; no medications
SH: Ex-smoker; charity volunteer
FH: None

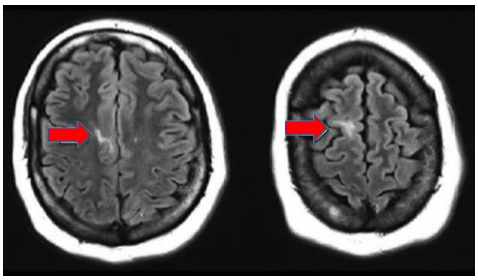
PRESENTATION
- **Acute** - Right-sided **headache**. - Nausea, vertigo, vomiting. - Next day new-onset **seizures**. - **Lower limb** weakness and **loss of bladder and bowel function**.

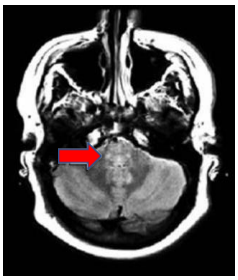
Investigations

Blood: MOG-ab positive
CSF: Unremarkable

MRI: LETM,
brainstem and brain lesions







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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES
- **Acute** - Right-sided **headache**. - Nausea, vertigo, vomiting. - Next day new-onset **seizures**. - **Lower limb** weakness and **loss of bladder and bowel function**.	- Treated with 3 days of IVMP. - Back to full power and walking unaided within a few weeks. - Persistent bladder and erectile dysfunction. ISC

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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES	LONG TERM TREATMENT AND OUTCOMES
- **Acute** - Right-sided **headache**. - Nausea, vertigo, vomiting. - Next day new-onset **seizures**. - **Lower limb** weakness and **loss of bladder and bowel function**.	- Treated with 3 days of IVMP. - Back to full power and walking unaided within a few weeks. - Persistent bladder and erectile dysfunction. ISC	- After acute treatment he was maintained on low dose oral steroids for 1 year. - **Sphincter dysfunction resolved over time.** - Currently asymptomatic. - Remained relapse free.

AQP4-Ab: Myelitis (NMOSD)

TM, 81yo F

PMH: On SSRI for depression.
Blindness one eye 2 years earlier
Breast cancer 4 years earlier

FH: None

PRESENTATION
- **Acute** - Generally unwell - Reduced sensation and power in legs - >> arms - Loss of bladder and bowel function. - **Bed bound** - Unable to swallow safely - Respiratory difficulty - **Admitted to ITU**

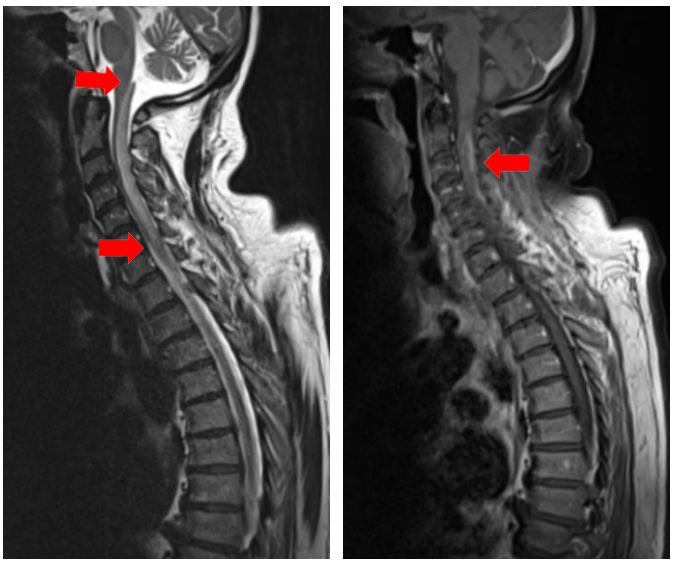
Investigations

Blood: *AQP4-ab positive*
ANA positive
Low sodium

CSF: *20 WBC (Lymh)*

MRI: LETM – extending from medulla

Blindness thought to be ON



post- gad enhancement

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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES
- **Acute** - Generally unwell - Reduced sensation and power in legs - >> arms - Loss of bladder and bowel function. - **Bed bound** - Unable to swallow safely - Respiratory difficulty - **Admitted to ITU**	- Treated with 5 days of IVMP and **PLEX** - Slow improvement over months - Persistent limb weakness and sphincter dysfunction - **Wheelchair bound >> Rehabilitation**

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- **Acute** - Generally unwell - Reduced sensation and power in legs - >> arms - Loss of bladder and bowel function. - **Bed bound** - Unable to swallow safely - Respiratory difficulty - **Admitted to ITU**	- Treated with 5 days of IVMP and **PLEX** - Slow improvement over months - Persistent limb weakness and sphincter dysfunction - **Wheelchair bound >> Rehabilitation**	- Maintained on low dose oral steroids - Started immunosuppressive agent. - **Wheelchair bound and catheter** - Remained relapse free - No recurrence of cancer - Has other morbidities

AQP4-Ab: Myelitis (NMOSD)

TM, 40 yo F

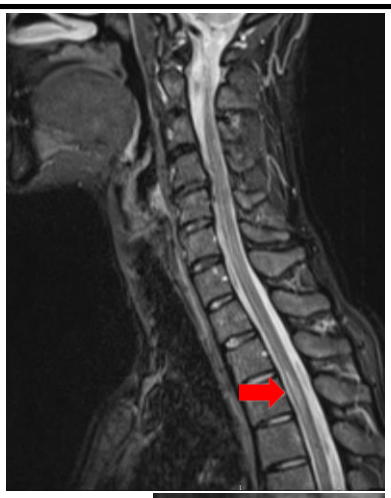
PMH: **Vomiting and hiccups for 5 we**eks, 3 months earlier; spontaneously resolved. No medications
SH: Business
FH: None

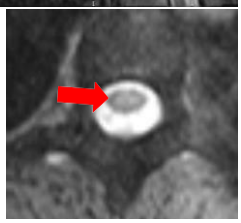
PRESENTATION
- **Acute** - Tingling sensation one side of the trunk and legs - Reduced sensation in legs (R>L)

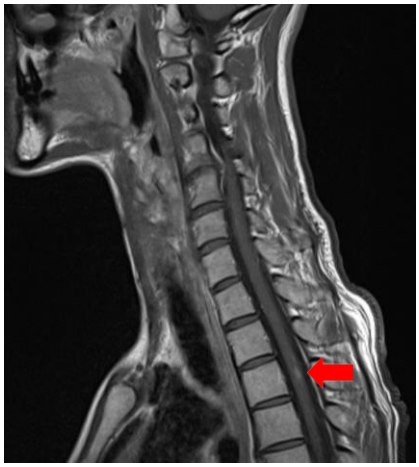
Investigations

Blood: *AQP4-ab positive*
ANA positive
CSF: ND

MRI: Short lesion (thoracic, central).
Normal brain/brainstem







post gad enhancement

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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES
- **Acute** - Tingling sensation one side of the trunk and legs - Reduced sensation in legs (R>L)	- Treated with high dose oral MP - Symptoms completely subsided 3 months

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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES	LONG TERM TREATMENT AND OUTCOMES
- **Acute** - Tingling sensation one side of the trunk and legs - Reduced sensation in legs (R>L)	- Treated with high dose oral MP - Symptoms completely subsided 3 months	- Maintained on low dose oral steroids - Started immunosuppressive agent. - Remained well and relapse free.

SLE/SS Encephalomyelitis

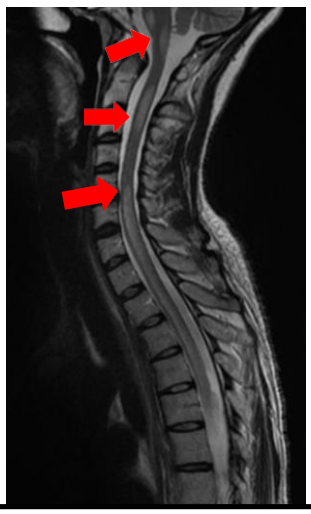
RA, 37 yo F

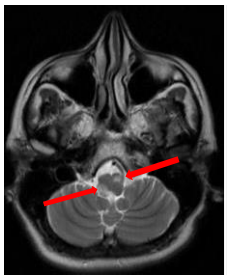
PMH: **3 month history of progressive, significant, rheumatological and systemic symptoms**
FH: Autoimmune thyroid disease

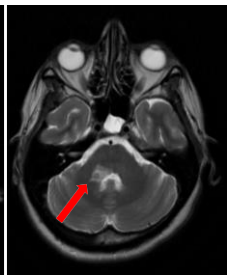
PRESENTATION
- **Subacute - stepwise** - Tingling sensation in the face - **Double vision** - Vertigo, vomiting - Tingling in the and legs - Mild limb weakness - Reduced sensation in legs and trunk (up to T3) - **Paraplegic** - **Sphincter dysfunction**

Investigations

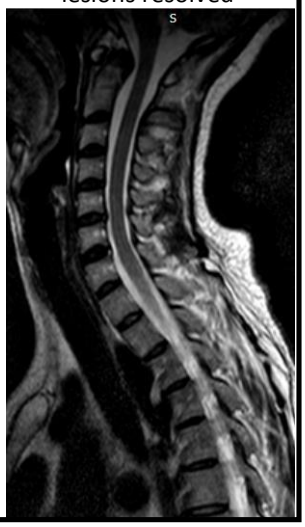
*Blood: ANA, DS-DNA, ENA, a*nti-SSA, anti-SSB *positive*
CSF: WCC 15 (Lymph); glucose normal; protein 0.9 g/L
MRI: Brainstem T2 lesions
LETM (patchy throughout cord)







Brainstem and cervical lesions resolved



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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES
- **Subacute - stepwise** - Tingling sensation in the face - **Double vision** - Vertigo, vomiting - Tingling in the and legs - Mild limb weakness - Reduced sensation in legs and trunk (up to T3) - **Paraplegic** - **Sphincter dysfunction**	- **Treated with high dose IVMP** - High dose oral steroid - PLEX - **Rituximab** - Brainstem symptoms resolved in 3 weeks.

SLE/SS Encephalomyelitis

RA, 37 yo F

PMH: **3 month history of progressive, significant, rheumatological and systemic symptoms**
FH: Autoimmune thyroid disease

PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES	LONG TERM TREATMENT AND OUTCOMES
- **Subacute - stepwise** - Tingling sensation in the face - **Double vision** - Vertigo, vomiting - Tingling in the and legs - Mild limb weakness - Reduced sensation in legs and trunk (up to T3) - **Paraplegic** - **Sphincter dysfunction**	- **Treated with high dose IVMP** - High dose oral steroid - PLEX - **Rituximab** - Brainstem symptoms resolved in 3 weeks.	- Maintained on oral steroids (reducing dose slowly) and hydroxychloroquine - **Rituximab** - **Remained paraplegic and with catheter.**

GFAP-Ab positive Meningo-encephalomyelitis

GH, 62 yo F

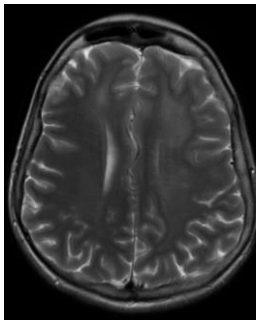
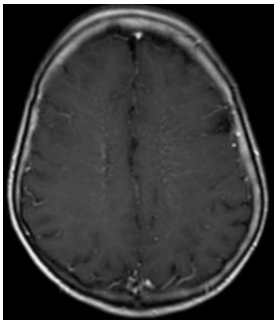
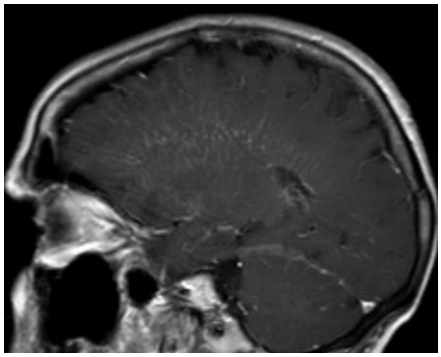
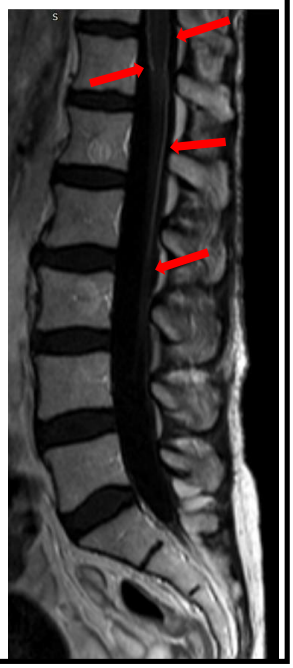
PMH: High BP
FH: none

PRESENTATION
- **Subacute – progressive** - **Memory** deficits - Poor concentration - **Seizures** - Mild mobility problems (occasional falls); leg weakness and increased tone

Investigations

Blood: GFAP-Ab positive
CSF: WCC 25 (Lymph); glucose normal; protein 0.65 g/L
CSF: GFAP-Ab positive

MRI: Brain – white matter diffused lesions with ***characteristic linear perivascular enhancement***
Spinal cord - Subtle T2 signal in the conus and nerve roots; ***linear enhancement of meninges and nerve roots.***

GFAP-Ab positive Meningo-encephalomyelitis

GH, 62 yo F

PMH: High BP
FH: none

PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES
- **Subacute – progressive** - **Memory deficits** - Poor concentration - **Seizures** - Mild mobility problems (occasional falls); leg weakness and increased tone	- Treated with high dose IVMP - High dose oral steroid - PLEX - **Improved** significantly of all symptoms

GFAP-Ab positive Meningo-encephalomyelitis

GH, 62 yo F

PMH: High BP
FH: none

PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES	LONG TERM TREATMENT AND OUTCOMES
- **Subacute – progressive** - **Memory deficits** - Poor concentration - **Seizures** - Mild mobility problems (occasional falls); leg weakness and increased tone	- Treated with high dose IVMP - High dose oral steroid - PLEX - **Improved** significantly of all symptoms	- Maintained on reducing dose oral steroids - **Relapsed when reached 5 mg a day** - **Increased steroid dose with improvement** - **Started immunosuppression.** - Malignancy surveillance

GlyR-Ab: Encephalomyelitis (PERM)

LB, 36yo F

PMH: None
SH: Teacher
FH: None

PRESENTATION
- **Subacute** - Axial and limb **rigidity** - Stimulus-sensitive myoclonus. - **Startle** - **Episodic apnoea** - Several **admissions to ITU**

Investigations

Blood: GlyR-Ab positive
CSF: GlyR-Ab positive
CSF: unremarkable

MRI: Brain – small number of non-specific white matter lesions
Cord - ND (claustrophobia and obesity)

EMG: continuous motor activity at rest

*Whole body scans: 53 mm left **ovarian teratoma***

GlyR-Ab: Encephalomyelitis (PERM)

LB, 36yo F

PMH: None
SH: Teacher
FH: None

PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES
- **Subacute** - Axial and limb **rigidity** - Stimulus-sensitive myoclonus. - **Startle** - **Episodic apnoea** - Several **admissions to ITU**	- **Several courses** of 5 days of IVMP - PLEX - IVIG - **Oophorectomy** - **Rituximab** - Some improvement, but: - Wheelchair bound - **Some episodes of rigidity and apnoea**

GlyR-Ab: Encephalomyelitis (PERM)

LB, 36yo F

PMH: None
SH: Teacher
FH: None

PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES	LONG TERM TREATMENT AND OUTCOMES
- **Subacute** - Axial and limb rigidity - Stimulus-sensitive myoclonus. - Startle - Ataxia - Episodic apnoea - Several admissions to ITU	- **Several courses** of 5 days of IVMP - PLEX - IVIG - **Oophorectomy** - **Rituximab** - Some improvement, but: - Wheelchair bound - **Some episodes of rigidity and apnoea**	- Maintained on high dose oral steroids - Rituximab - IVIG when required - Ongoing, less frequent, episodes of rigidity and apnoea - **Wheelchair bound** - **Severe depression**

CRMP5-Ab: Myelopathy

BM, 59yo M

PMH: High BP
Blindness one eye 2 years earlier
Chronic mucocutaneous candidiasis
SH: Financial accountant
FH: Sister had thymoma

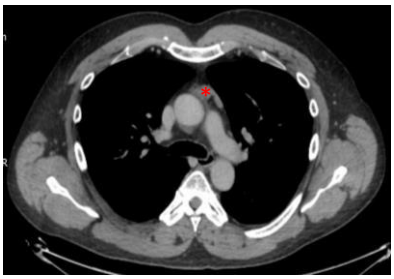
PRESENTATION
- **Acute - Subacute** - Tingling sensation in the legs and trunk. - Leg weakness – unaided   - >> support - Sphincter dysfunction

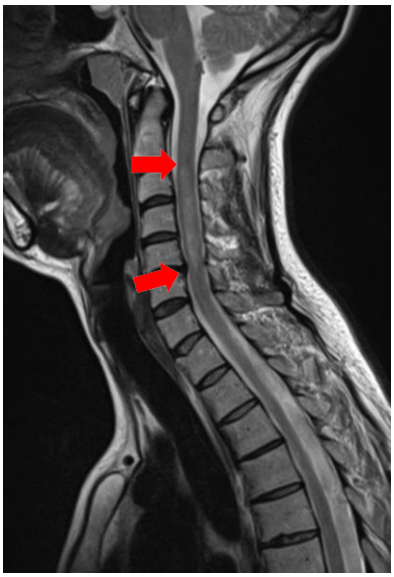
Investigations

Blood: CRMP5-Ab positive (found later)
Interleukin abs
CSF: WCC 12; glucose normal; protein 0.75 g/L

MRI: cervical LETM

*CT chest: thymoma (*B2/B3, STAGE 2)





CRMP5-Ab: Myelopathy

BM, 59yo M

PMH: High BP
Blindness one eye 2 years earlier
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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES
- **Acute - Subacute** - Tingling sensation in the legs and trunk. - Leg weakness – unaided - >> support - Sphincter dysfunction	- Treated with 3 days of IVMP. - Moderate improvement of all neurological deficits - Ongoing bladder sphincter dysfunction - Thymectomy & radiotherapy

CRMP5-Ab: Myelopathy

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Chronic nail candidiasis
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PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES	LONG TERM TREATMENT AND OUTCOMES
- Acute - Subacute - Tingling sensation in the legs and trunk. - Leg weakness – unaided - >> support - Sphincter dysfunction	- Treated with 3 days of IVMP. - Moderate improvement of all neurological deficits - Ongoing bladder sphincter dysfunction - Thymectomy & radiotherapy	- Maintained on low reducing dose oral steroids. - One further myelitis relapse - Started immunosuppression - Remained stable neurologically - No thymoma recurrence

Seronegative myeloradiculopathy (Post-lymphoma treatment)

AG, 44yo F

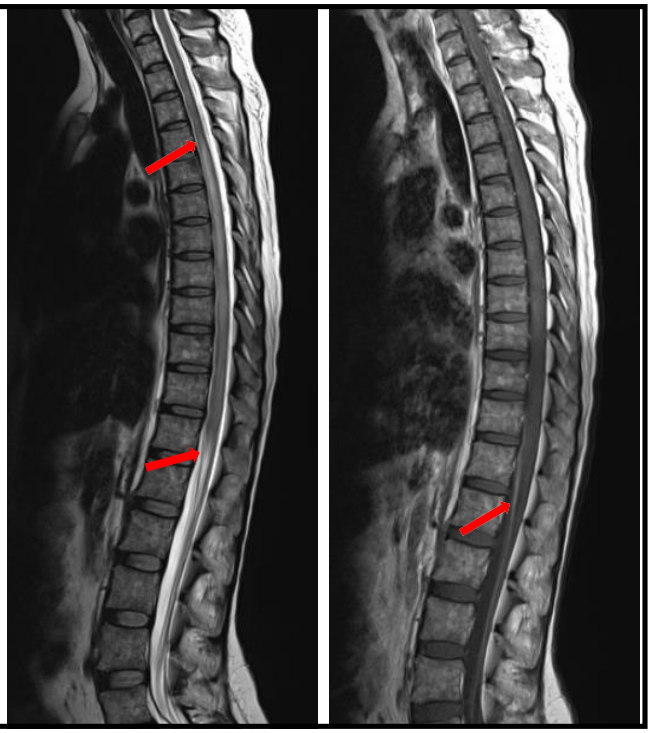
PMH: **Non-Hodgkin Lymphoma – treated** with rituximab + chemotherapy

PRESENTATION
- **Subacute** - leg weakness and reduced sensation. - assisted walking - = Polyradiculopathy lower limbs - Improved with IVIG and oral steroids - at low dose steroid: - … **acute severe leg weakness, reduced sensation and sphincter dysfunction**

Investigations

Blood: seronegative all relevant abs
CSF: No cells, glucose normal; protein 1.2 g/L
No evidence of lymphoma cells

MRI: LETM with Gad enhancement mainly in the ***meninges and nerve roots***



Seronegative myeloradiculopathy (Post-lymphoma treatment)

AG, 44yo F

PMH: Non-Hodgkin Lymphoma – treated with rituximab + chemotherapy

PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES
- **Subacute** - leg weakness and reduced sensation. - assisted walking - = Polyradioculopathy lower limbs - Improved with IVIG and oral steroids - at low dose steroid: - … **acute severe leg weakness, reduced sensation and sphincter dysfunction**	- IVIG - High dose IVMP - Very little improvement. - **Wheelchair bound and catheter**

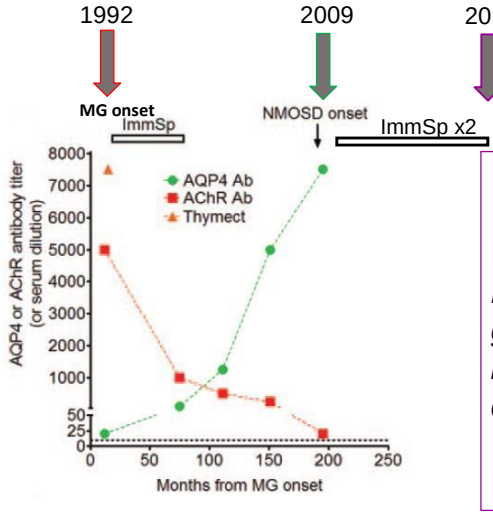
Seronegative myeloradiculopathy (Post-lymphoma treatment)

AG, 44yo F

PMH: Non-Hodgkin Lymphoma – treated with rituximab + chemotherapy

PRESENTATION	SHORT TERM TREATMENT AND OUTCOMES	LONG TERM TREATMENT AND OUTCOMES
- **Subacute** - leg weakness and reduced sensation. - assisted walking - = Polyradioculopathy lower limbs - Improved with IVIG and oral steroids - at low dose steroid: - … **acute severe leg weakness, reduced sensation and sphincter dysfunction**	- IVIG - High dose IVMP - Very little improvement. - **Wheelchair bound and catheter**	- Maintained on oral steroids - Stable neurologically and haematologically, but: - **Wheelchair bound** - **Catheter**

Multiple autoimmune diseases, immunotherapies and malignancies



Infections

Lung mass - *Lymphomatoid granulomatosis (EBV driven lymphoproliferative condition)* >>>>> ***Rituximab***

Papillary carcinoma THY 5

M I Leite et al
Neurology® 2012;78:1601-1607

Final thoughts / messages

- Autoimmune disease affecting spinal cord (myelitis) may present as an isolated neurological event or as part of a diffused /multifocal neurological and or systemic condition (autoimmune or malignancy).
- Non spinal cord features (neurological, other organs or systemic) may help to identify the cause of myelitis.
- Demographic, clinical and radiological characteristics help to define overall features of certain diseases and predict associated autoantibody and even the outcome.
- Prompt acute treatment is sometimes required when only clinical and imaging findings are available.

Final thoughts / messages

- Autoantibody tests are very helpful (in some cases, e.g. GlycR ab, CSF increases certainty)
- Seronegative patients require careful differential diagnosis work-up
- The spectrum and concept of paraneoplastic illnesses is changing and expanding:
  - antibodies to surface cell antigens may be associated with tumours
  - tumours may cause autoimmunity
  - anti-tumour therapies may contribute to autoimmunity
  - Immunotherapies may contribute to malignancy

Thank you very much

Current Neurology and Neuroscience Reports (2018) 18: 3
https://doi.org/10.1007/s11910-018-0810-1

NEURO-ONCOLOGY (LE ABREY, SECTION EDITOR)

Neurological Adverse Events Associated with Immune Checkpoint Inhibitors: Diagnosis and Management

Christophoros Astaras[1] · Rita de Micheli[1] · Bianca Moura[1] · Thomas Hundsberger[2] · Andreas F. Hottinger[3]