



Rebound syndrome in two patients with Multiple Sclerosis after cessation of Fingolimod treatment



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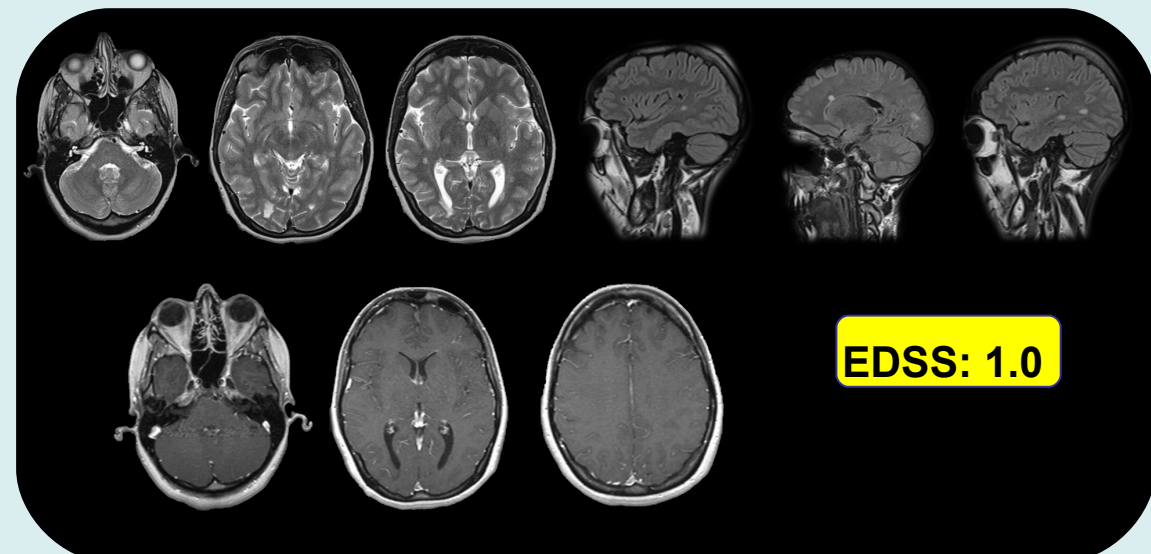
Female, 31 years 2007 Diagnosis of Multiple Sclerosis Relapsing and Remitting

Betaferon March 2007 – December 2007
Copaxon February 2008 – December 2008
Rebif 22 January 2009 – January 2010
Avonex February 2011 – April 2012

→ liver dysfunction
→ 2 sensitive relapses
→ leukopenia
→ relapse(diplopia)

Test Stratify: + per JCV-Ab high title

Fingolimod January 2013 – January 2015

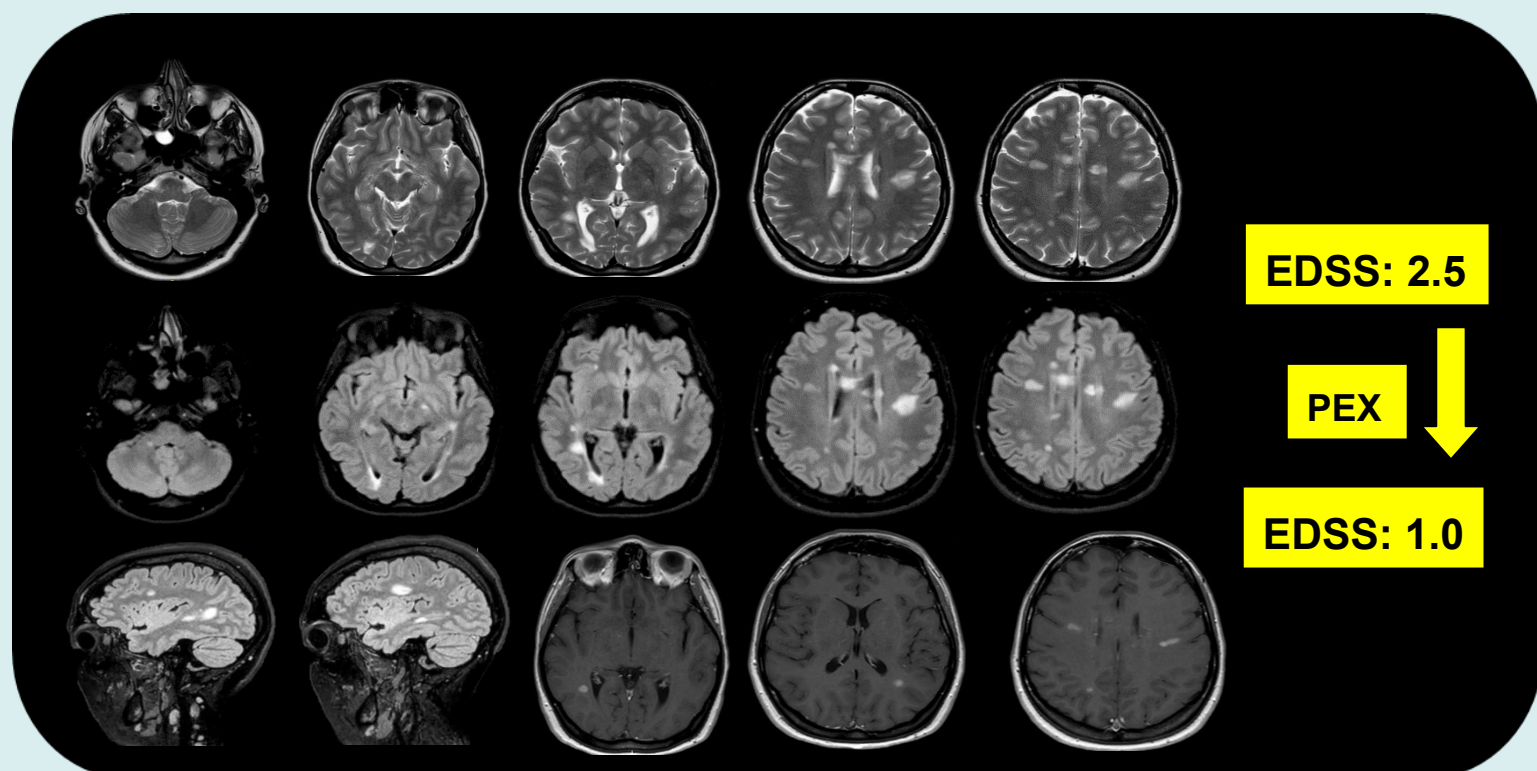


Due to the clinical-radiological stability the patient decides to **stop Fingolimod** to attempt pregnancy **January 2015**

March 2015 (no pregnancy ongoing)

relapse:
right sensitive hemisindrome
urinary retention

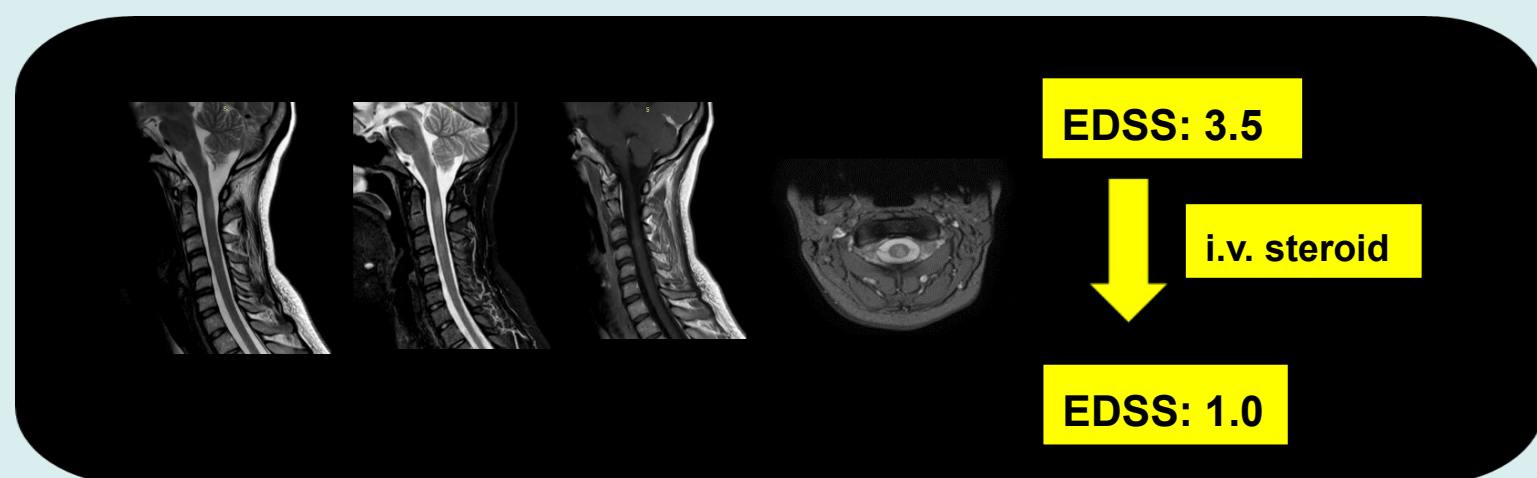
Brain RM : 10 new lesions
left cerebral peduncle, temporal pole, right and left corona radiata, corpus callosum, left cella media sn, vertex
8 Gd+ lesions



April 2015

relapse:
left sensitive hemisindrome
urinary retention

Spinal MRI:
large C1-C2 lesion
new Gd+ lesion on C4 segment



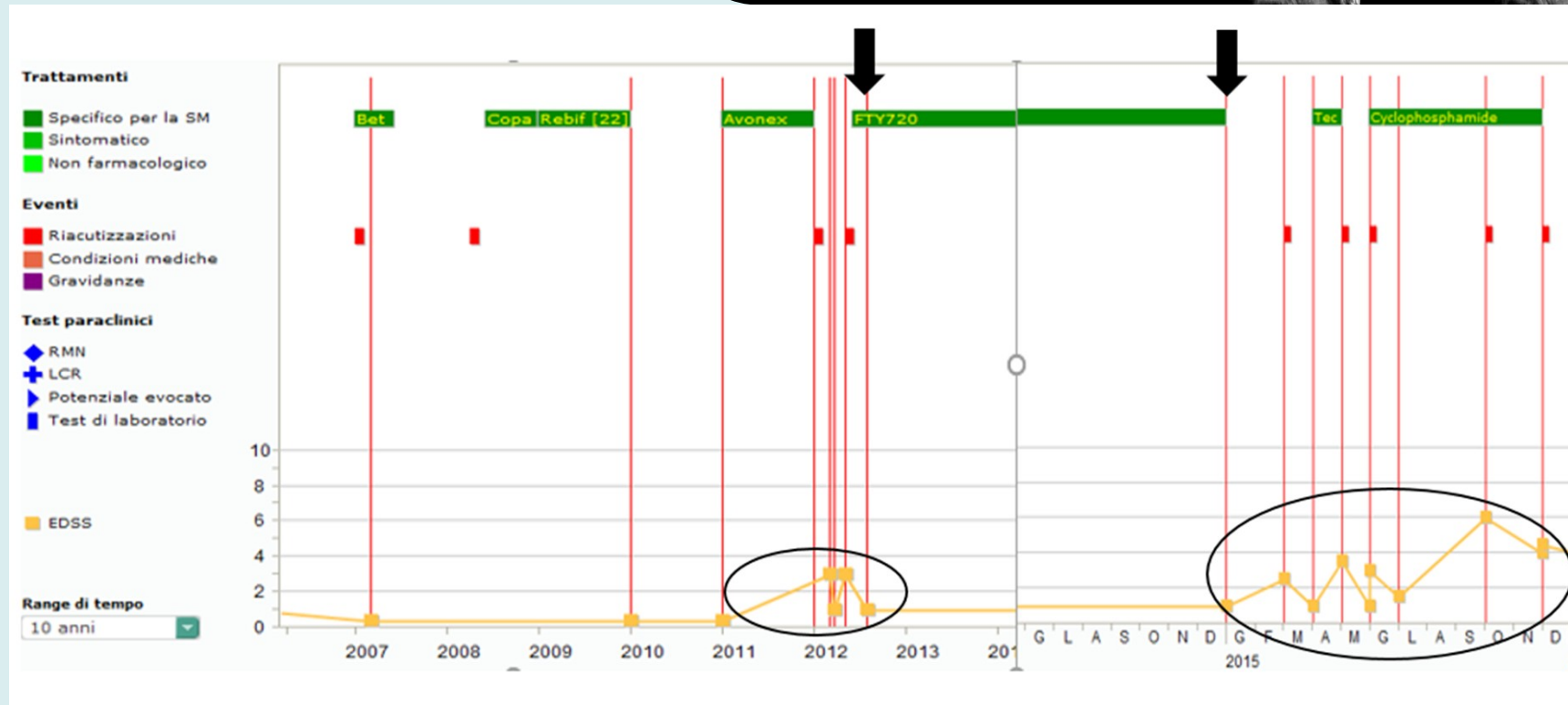
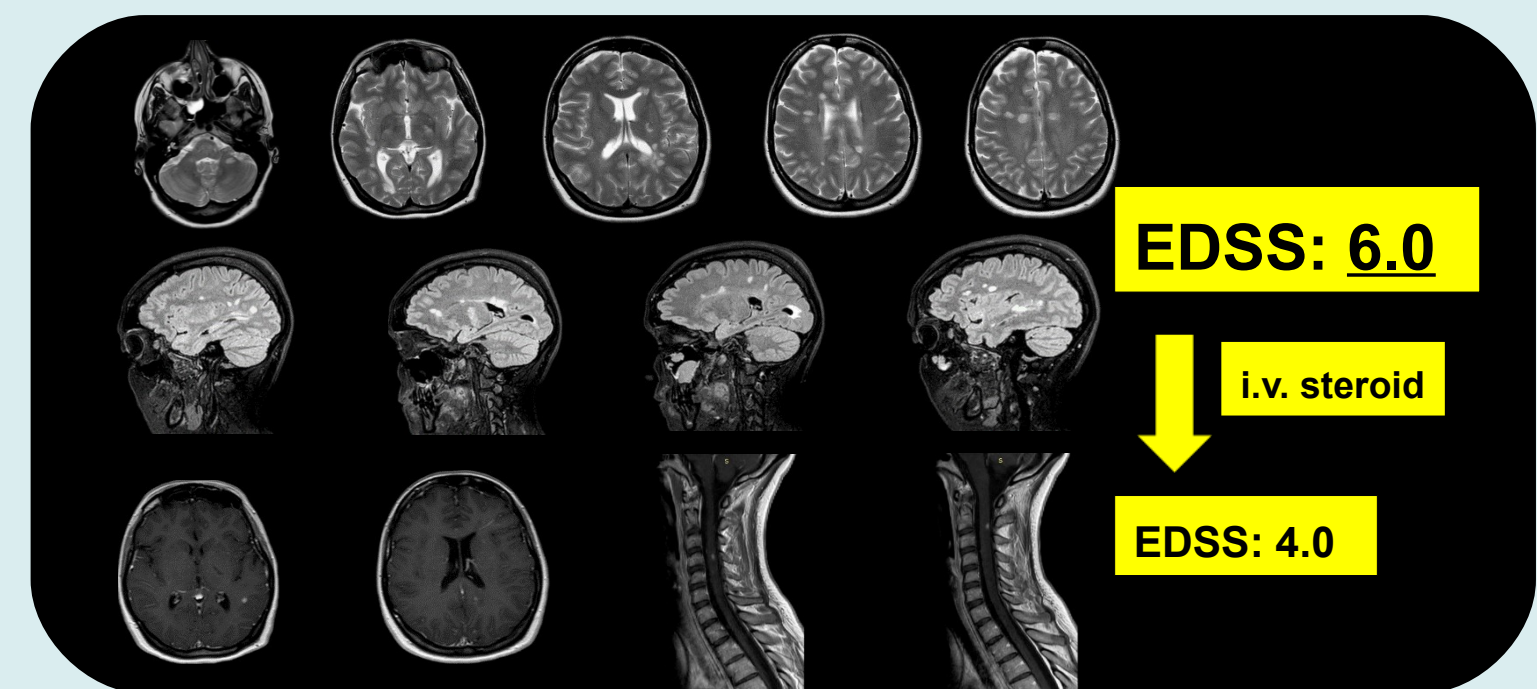
April 2015 Dimethyl-fumarate → **Maggio 2015 spinal cord relapse, with new Gd+ lesion** EDSS: 3.0

May 2015 Cyclophosphamide 1g/m2 i.v.

October 2015

relapse:
left sensori-motor hemisindrome
urinary retention

Brain and Spinal MRI:
new T2/FLAIR lesions in brain and spinal cord
new Gd+ lesions (at least 4)



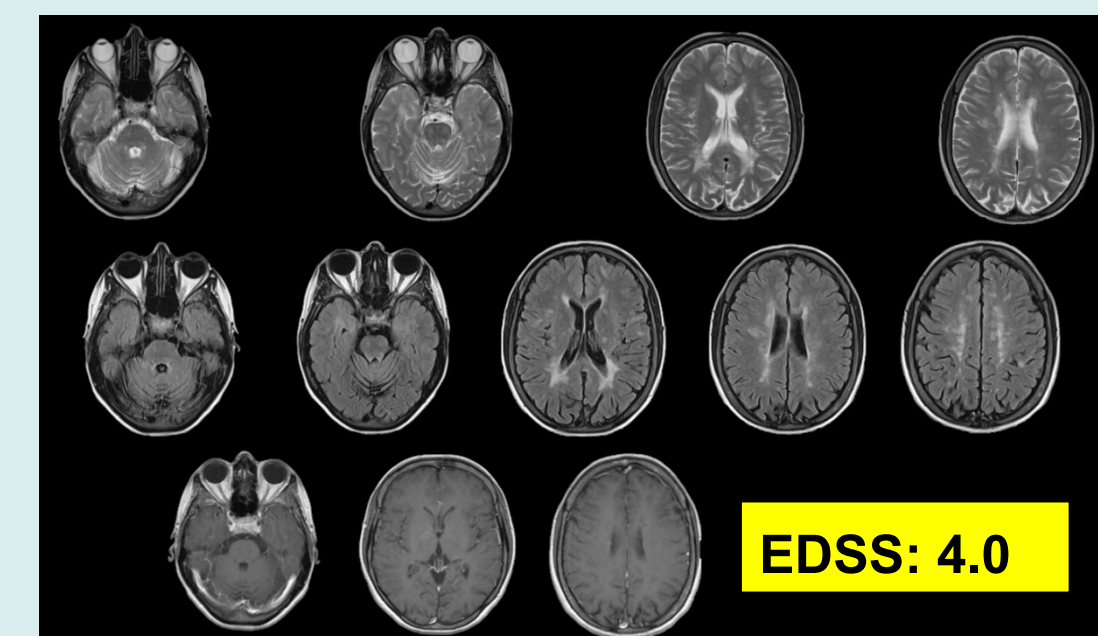
Female, 49 years 1997 Diagnosis of Multiple Sclerosis Relapsing and Remitting

Avonex 1998 – 2002
Copaxon 2002 – 2006

→ flue-like syndrome
→ 3 relapses

Natalizumab 2007-2011
Fingolimod 2011 – Gennaio 2016

→ JCV-Ab high title
→ 1 motor spinal relapses



Due to the persistence of inflammatory activity on the Secondary Progressive phase, the patient performs preliminary exams to start therapy with Alemtuzumab

Pap test shows **cervical intra-epithelial neoplasia**, probably malignant

Urgently, a colposcopy is performed

March 2016

(25 days after Fingolimod withdrawal)

→ **severe spinal cord relapse** presenting with:
- paraparesis,
- dorsal sensory level
- urinary retention EDSS: 6.5

→ Dorsal MRI: new Gd+ lesion on D3-D4 segment

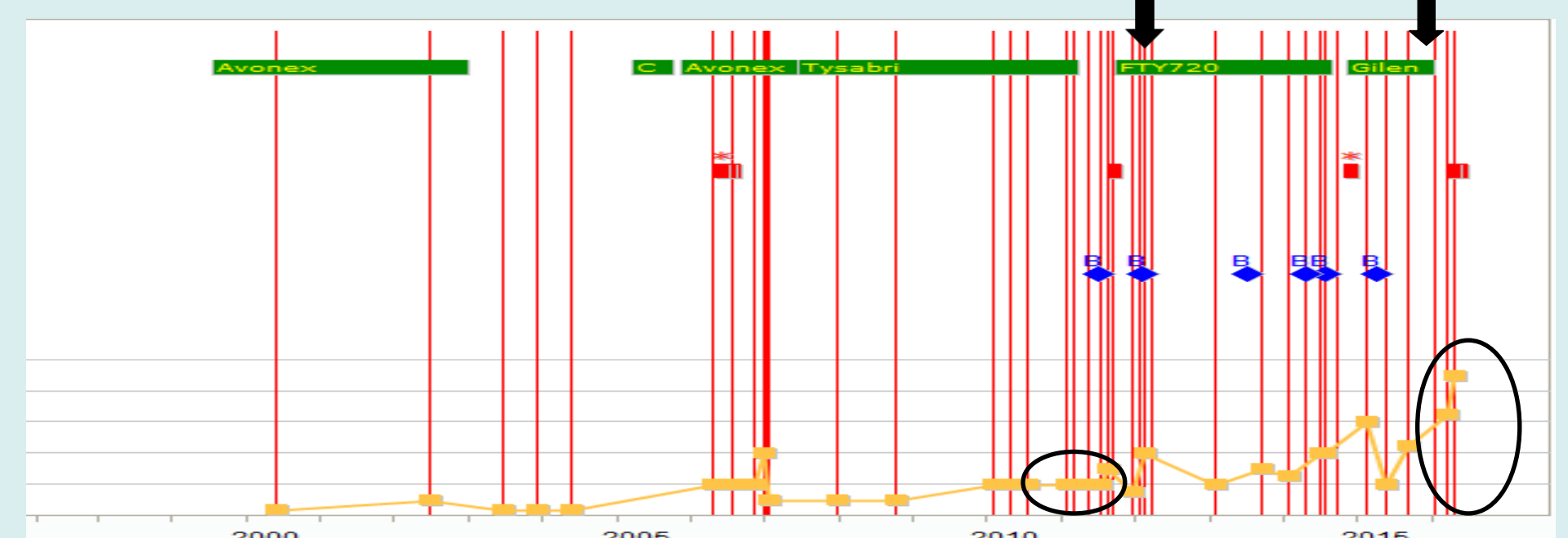
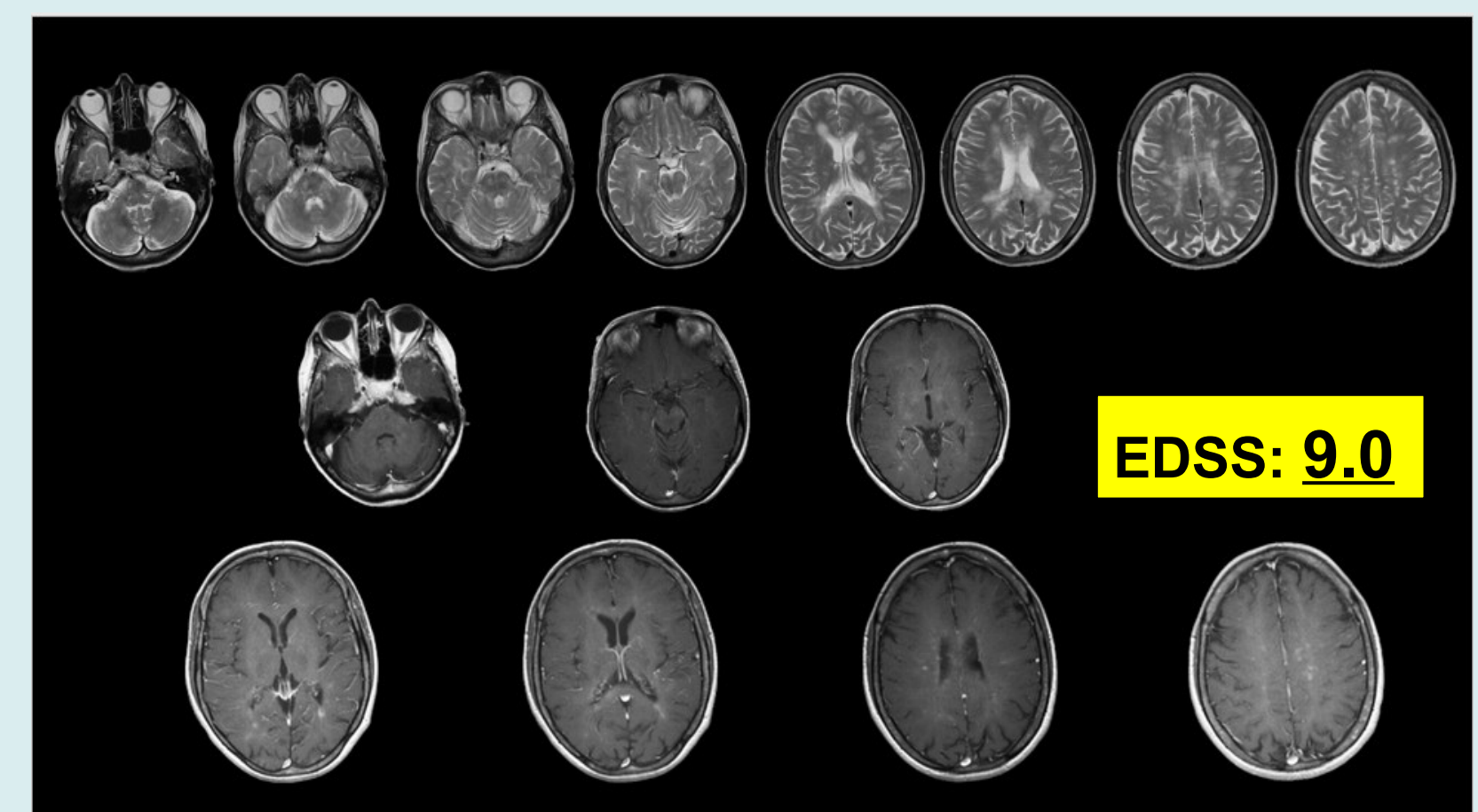
i.v. steroid

no clinical response

PEX

At the third cycle of PEX (21 April 2016) neurological examination rapidly worsens with:

-left ptosis
-complete ophthalmoplegia
-dysarthria
-paraplegia



The literature lacks a clear and univocal definition of rebound activity
According to Bertolotto et al., *Neurol Ther* 2015, a definition of rebound activity may be as follows (at least two):

- an ARR increase in comparison to pre-DMT disease course
- one or more severe relapses with sustained disability progression (one-step EDSS increase)
- three or more new large T2 lesions and/or Gd-enhancing lesions in the MRI
- new tumor-like demyelinating lesions in the MRI

To date, 22 cases of rebound syndrome after Fingolimod withdrawal are described in the literature

The most appropriate therapy for this phenomenon is a challenge

January 2016 Alemtuzumab

Brain MRI at 6 mo follow-up:
-no new T2/FLAIR lesions
-no Gd+ lesions

At 8 mo from the 1 cycle:
-spinal cord relapse, treated with intravenous high dose steroid therapy EDSS: 4.0

April 2016 AHST

Between the induction and the conditioning phase:
-spinal cord relapse, treated with intravenous high dose steroid therapy and followed by BEAM regimen

Brain MRI at the end of AHST:
-no new T2/FLAIR lesions
-no Gd+ lesions EDSS: 6.0