

Neurologist-in-training: Multiple sclerosis

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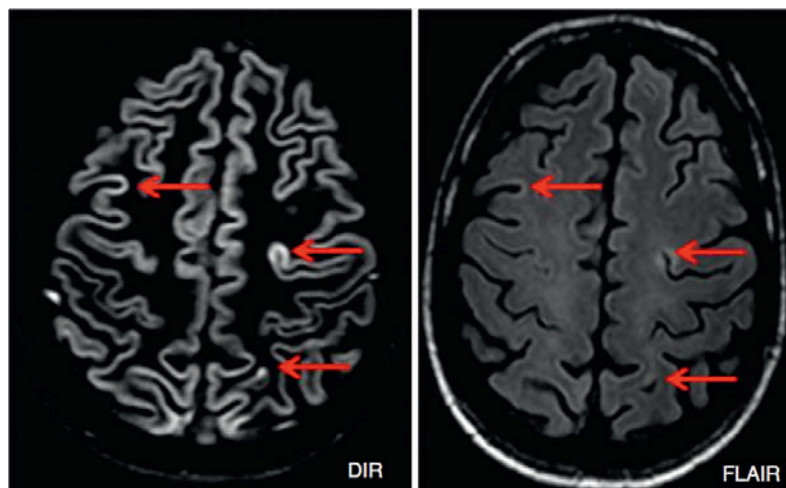
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Questions

1. Which of the following findings in a multiple sclerosis (MS) patient should arouse the strongest possible suspicion of an alternative diagnosis?
 - A Contrast enhancement of the meninges on T1 weighted images.
 - B Contrast enhancing periventricular lesions on T1 weighted images.
 - C Hyperintense lesions in proton-density weighted images of the spinal cord.
 - D Hyperintense cortical lesions on double inversion recovery sequences.
 - E Hypointense lesions on T1 weighted images.
2. A 20-year-old woman presents with a 2 weeks' history of reduced visual acuity (0.2) of the left eye with pain during eye movements. No additional findings on neurological examination, no previous history of neurological symptoms or complaints. Cerebrospinal fluid (CSF) analysis revealed 10 cells/ μ l, normal protein and 5 oligoclonal bands present only in CSF. Other results of serum and CSF analysis were normal and not suggestive of infection. Cranial MRI revealed 4 T2-hyperintense lesions. One of the lesions is in the cerebellum and shows contrast enhancement, the other three are located periventricularly without contrast enhancement. Which statement(s) is/are correct?
 - 1 Patient has a CIS suggestive of MS; dissemination in time is not fulfilled.
 - 2 Patient fulfills the present McDonald criteria for relapsing-remitting MS.
 - 3 Patient has optical neuritis and current guidelines do not recommend starting disease-modifying treatment.
 - 4 Fingolimod treatment is licensed in Switzerland for the treatment of relapsing-remitting MS but not for CIS.
 - A 1 + 3 are correct.
 - B 2 + 4 are correct.
 - C 1 + 4 are correct.
 - D Only 2 is correct.
3. Which of the statements regarding MS treatment is incorrect?
 - A Previous treatment with mitoxantrone is not a contra-indication for natalizumab treatment.
 - B The duration of natalizumab treatment has an influence on the risk of PML.
 - C Natalizumab is licensed as first line medication in specified cases of RR MS.
 - D Antibodies against natalizumab have no influence on the effectiveness of natalizumab treatment.
4. Which of the following side-effects are most probably not associated with fingolimod treatment?
 - A Macular oedema.
 - B Tachycardia.
 - C Lower respiratory tract infection.
 - D Lymphocytopenia.
 - E Liver enzyme elevation.
5. According to the OLYMPUS trial, which patients with primary progressive MS may benefit most?
 - 1 Older patients, from off-label treatment with rituximab.
 - 2 Younger patients.
 - 3 Patients with gadolinium-enhancing lesions.
 - 4 Patients with oligoclonal bands in CSF.
 - A Only 1 is correct.
 - B 2 + 3 + 4 are correct.
 - C 2 + 3 are correct.
 - D 1 + 3 are correct.
 - E All are correct.
6. Which statement is incorrect?
 - A The average age at presentation for primary progressive multiple sclerosis (PPMS) is 40–50 years.
 - B The most common course in PPMS patients is slowly progressive myelopathy.
 - C According to present McDonald criteria oligoclonal bands or elevated IgG index in CSF are mandatory for the diagnosis of PPMS.
 - D Contrast enhancing brain lesions are less frequent in PPMS in comparison with relapsing-remitting MS patients.
 - E The disability progression of patients with secondary progressive MS from the onset of the progressive phase is similar to that of PPMS patients.
7. What is, according to current literature, the conversion rate of the radiologically isolated syndrome to MS within 5 years?
 - A <5%
 - B 6–15%

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Figure 1 Comparing FLAIR and DIR sequences of cortical lesions from a single patient at the same section location (by courtesy of Dr. V. Sethi and Prof. D.H. Miller, UCL).



- C 30–40%
- D >50%

8. Which statement is incorrect?

- A Acute disseminated encephalomyelitis (ADEM) is a monophasic demyelinating disease.
- B ADEM is more likely than MS to occur in older individuals.
- C In most cases of ADEM an infection or vaccination precedes the neurological symptoms by 1–3 weeks.
- D Encephalopathic symptoms are typical of ADEM.
- E ADEM variants can be fulminant and devastating with haemorrhagic lesions.

Answers and comments

Answer 1

A is correct.

The diagnosis of MS should be questioned when clinical or laboratory findings are atypical. Contrast enhancing periventricular lesions on T1 weighted images are typical findings in MS patients with active disease. Most new enhancing lesions initially appear hypointense on T1 weighted images due to oedema and early demyelination. In approximately 60% of such lesions the T1 signal gradually returns to isointense after months. The persistent T1-weighted hypointense lesions are called chronic black holes and represent areas of insufficient repair and remyelination [1–9]. The double inversion recovery sequence (DIR) is a relatively new MRI sequence which was introduced in 1998 and distinguishes better between neocortex and the subcortical white matter by suppressing both the white matter and the CSF signal [10]. On DIR images cortical MS lesions appear hyperintense relative to the surrounding grey matter (fig. 1). Meningeal contrast enhancement is not typical of MS and should prompt suspicion of an alternative diagnosis, e.g., neuro-sarcoidosis.

Answer 2

B is correct.

This patient fulfils the 2010 revised McDonald criteria [11] for relapsing-remitting MS.

According to these new criteria it is possible to demonstrate dissemination in time with a single MRI if this shows gadolinium enhancing and non-enhancing MS lesions simultaneously. To fulfil this criterion it is necessary that the gadolinium enhancing lesion be not the symptomatic one. In the case presented the patient had optic neuritis and the enhancing lesion was located in the cerebellum, fulfilling the criteria of dissemination in time. In the 2001 and 2005 McDonald criteria a positive CSF finding could be used to reduce the MRI requirements for reaching the dissemination in space criteria. According to 2001 and 2005 McDonald criteria dissemination in space could be demonstrated in a patient with one relapse and two MRI detected lesions consistent with MS, if the patient had oligoclonal bands by isoelectric focusing different from any such bands in serum or by an increased IgG index. The revised 2010 McDonald criteria do not allow weaker MRI requirements in CSF-positive patients. On the other hand, 9 or more brain lesions are no longer mandatory to fulfil the dissemination in space criteria (Barkhof-Tintore criteria). Dissemination in space can be demonstrated by at least 1 lesion in at least 2 of the following 4 areas: periventricular, juxtacortical, infratentorial or spinal cord (Swanton criteria). It is important to note that the symptomatic lesions do not contribute to the total lesion count if the patient has a brainstem or spinal cord syndrome. In contrast to the European Union, fingolimod is licensed in Switzerland and USA as first line medication for MS.

Answer 3

D is correct.

Natalizumab can be administered to patients with prior mitoxantrone treatment. However, the duration of natalizumab treatment, the presence of anti-JCV antibodies in the serum and prior use of immunosuppressants such as mitoxantrone are known risk factors for the development of progressive multifocal leukoencephalopathy (PML) in MS patients treated with natalizumab. Patients at lowest risk of developing PML are those who tested negative for anti-JCV antibodies, with an estimated risk of 0.11 per 1000 patients (95% confidence interval 0–0.59). Patients on natalizumab treatment for more than 2 years, prior immunosuppressive treatment and positive anti-JCV antibody status have an estimated PML risk of 7.8 per 1000 patients (95% confidence interval 5.2–11.3) [12–14]. Natalizumab is not only licensed for patients who have failed to respond to therapy with interferon beta. It can be used as first line medication in patients with rapidly evolving severe relapsing-remitting MS, defined by the European Medical Agency as two or more disabling relapses in one year, and with one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI [15]. Anti-natalizumab antibodies had the potential to neutralise natalizumab in vitro. About 9–11% of

the patients receiving natalizumab developed antibodies at least once during treatment, 3–5% transiently and 6% persistently. The presence of antibodies was correlated with a higher incidence of infusion-related symptoms, a reduction in serum concentrations of natalizumab and reduced efficacy.

Anti-natalizumab antibodies should be tested in patients who are not responding to natalizumab or patients with infusion-related side effects. If positive, antibody testing should be repeated after 2–3 months. If antibodies to natalizumab persist, treatment should be discontinued [16–18].

Answer 4

B is correct.

Fingolimod sequesters lymphocytes in lymph nodes, preventing them from moving from the lymph nodes into the blood. This is the reason why after initiation of fingolimod treatment the blood lymphocyte counts decrease within one month. In the Phase III placebo-controlled trial bradycardia and atrioventricular blocks were the most common serious adverse events in fingolimod-treated patients [19]. These findings are transient and related in most cases to the first dose of the medication. After an unexplained sudden death in a patient within 24 hours of taking fingolimod, the European Medicines Agency started a review of fingolimod's cardiovascular safety in January 2012. Recently, on 20 April 2012, the agency issued new and stronger advice to improve management of the risk of adverse effects on the heart in MS patients on fingolimod. According to these recommendations doctors should not prescribe fingolimod to patients with a history of specified cardiovascular and cerebrovascular diseases or who take heart-rate lowering medication. If fingolimod is considered necessary in these patients, the advice of cardiologists should be sought and patients should be monitored at least overnight following the first dose. According to Swissmedic all patients starting fingolimod should undergo an ECG before receiving the first dose, and have blood pressure and pulse measurements every hour, followed by a second ECG six hours afterwards [20]. Macular oedema occurred in less than 1% of the patients and was reversible after discontinuation of fingolimod. Lower respiratory tract infections including bronchitis and pneumonia were also more frequent in patients treated with fingolimod compared with placebo. In up to 12.5% of the patients treated with fingolimod the transaminases increased to levels three times the upper limit of the normal range or more. However, in all patients these asymptomatic liver enzyme abnormalities returned to normal after discontinuing the drug [19].

Answer 5

C is correct.

Rituximab is a chimaeric anti-CD20 monoclonal antibody that depletes B cells. It is not licensed for the treatment of MS. Since it possesses demonstrated high efficacy in reducing disease activity in relapsing-remitting MS, rituximab can be used as an off-label treatment option for MS in certain clinical scenarios, and a humanised anti-CD20 monoclonal

antibody, ocrelizumab, is at a late stage of development for MS treatment. The OLYMPUS trial evaluated the efficacy of rituximab in patients with primary progressive (PP) MS. Using 2:1 randomisation, 439 PPMS patients received two infusions of either 1 g intravenous rituximab or placebo every 6 months for 2 years. The primary endpoint was the time to confirmed disease progression. Secondary endpoints were the change from baseline to week 96 in T2 lesion volume and total brain volume on MRI scans. Despite an overall negative result, a significant effect on confirmed disease progression was seen in a predetermined subgroup analysis of patients aged below 51 years and with one or more Gd-enhancing lesions on the baseline MRI [21].

Answer 6

C is correct.

Primary progressive (PP) MS, unlike relapsing-remitting MS, often presents at a later age and has an equal gender distribution. When comparing PPMS with secondary progressive MS, the progression of disability from the onset of the progressive phase is similar [22–24]. Oligoclonal bands or an elevated IgG index are not mandatory for the diagnosis of PPMS, although it is common. Although not formally mentioned in the revised 2010 McDonald criteria, a CSF examination is still strongly recommended to rule out alternative diagnoses. Formally, a patient with one year of disease progression (retrospectively or prospectively determined), one periventricular and two T2 lesions in the spinal cord would theoretically also qualify for the diagnosis of PPMS.

Answer 7

C is correct.

The widespread use of MRI has led to the unexpected detection of lesions that appear typical of MS in otherwise asymptomatic patients, the so-called radiologically isolated syndrome (RIS). In a prospective study of 53 women and 17 men with a radiologically isolated syndrome (30 patients with oligoclonal bands in CSF) Lebrun et al. found a clinical conversion rate of 33% during a mean follow-up of 5.2 years [25].

Answer 8

B is correct.

Acute disseminated encephalomyelitis (ADEM) is a monophasic condition characterised by multifocal inflammatory demyelinating lesions. ADEM is more common in children than adults. Typically ADEM is associated with recent vaccination or infections such as measles or varicella. ADEM can usually be distinguished from MS by a history of prior vaccination or infection and the rapid onset of multifocal symptomatic lesions. Alterations in consciousness and seizures are common in ADEM and rare in MS. Patients with ADEM more frequently have contrast enhancing lesions in comparison to MS and CSF analysis usually shows a more pronounced lymphocytic pleocytosis and more severe blood-CSF barrier disruption by elevated total protein

or the albumin quotient. In addition, oligoclonal bands are less frequent. Nevertheless, CSF analysis is of limited relevance for differentiation of ADEM from MS.

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References

- 1 van Waesberghe JH, van Walderveen MA, Castelijns JA, et al. Patterns of lesion development in multiple sclerosis: longitudinal observations with T1-weighted spin-echo and magnetization transfer MR. *AJNR Am J Neuroradiol*. 1998;19:675–83.
- 2 Bitsch A, Bruhn H, Vougioukas V, et al. Inflammatory CNS demyelination: histopathologic correlation with in vivo quantitative proton MR spectroscopy. *AJNR Am J Neuroradiol*. 1999;20:1619–27.
- 3 Bruck W, Bitsch A, Kolenda H, Bruck Y, Stiefel M, Lassmann H. Inflammatory central nervous system demyelination: correlation of magnetic resonance imaging findings with lesion pathology. *Ann Neurol*. 1997;42:783–93.
- 4 Karampekios S, Papanikolaou N, Papadaki E, et al. Quantification of magnetization transfer rate and native T1 relaxation time of the brain: correlation with magnetization transfer ratio measurements in patients with multiple sclerosis. *Neuroradiology*. 2005;47:189–96.
- 5 Levesque I, Sled JG, Narayanan S, et al. The role of edema and demyelination in chronic T1 black holes: a quantitative magnetization transfer study. *J Magn Reson Imaging*. 2005;21:103–10.
- 6 Otaduy MC, Callegaro D, Bacheschi LA, Leite CC. Correlation of magnetization transfer and diffusion magnetic resonance imaging in multiple sclerosis. *Mult Scler*. 2006;12:754–9.
- 7 van Waesberghe JH, van Buchem MA, Filippi M, et al. MR outcome parameters in multiple sclerosis: comparison of surface-based thresholding segmentation and magnetization transfer ratio histogram analysis in relation to disability (a preliminary note). *AJNR Am J Neuroradiol*. 1998;19:1857–62.
- 8 van Walderveen MA, Kamphorst W, Scheltens P, et al. Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. *Neurology*. 1998;50:1282–8.
- 9 van Walderveen MA, Barkhof F, Pouwels PJ, van Schijndel RA, Polman CH, Castelijns JA. Neuronal damage in T1-hypointense multiple sclerosis lesions demonstrated in vivo using proton magnetic resonance spectroscopy. *Ann Neurol*. 1999;46:79–87.
- 10 Bedell BJ, Narayana PA. Implementation and evaluation of a new pulse sequence for rapid acquisition of double inversion recovery images for simultaneous suppression of white matter and CSF. *J Magn Reson Imaging*. 1998;8:544–7.
- 11 Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292–302.
- 12 Sandrock A, Hotermans C, Richman S. Risk stratification for progressive multifocal leukoencephalopathy (PML) in MS patients: role of prior immunosuppressant use, natalizumab treatment duration, and anti-JCF antibody status. *Neurology*. 2011;76(Suppl 4):A248.
- 13 Per Soelberg Sørensen, Antonio Bertolotto, Gilles Edan, Gavin Giovannoni, Ralf Gold, Eva Havrdova, et al. Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. *Mult Scler*. 2012;18:143.
- 14 Kappos L, Bates D, Edan G, Eraksoy M, Garcia-Merino A, Grigoriadis N, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. *Lancet Neurol*. 2011;10(8):745–58.
- 15 European Medicine Agency, www.ema.europa.eu
- 16 Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354:899–910.
- 17 Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med*. 2006;354:911–23.
- 18 Calabresi PA, Giovannoni G, Confavreux C, et al. The incidence and significance of anti-natalizumab antibodies: Results from AFFIRM and SENTINEL. *Neurology*. 2007;69:1391–403.
- 19 Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al.; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387–401.
- 20 Press release, European Medicines Agency, www.ema.europa.eu
- 21 Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, Hauser S, Waubant E, Vollmer T, Panitch H, Zhang J, Chin P, Smith CH; OLYMPUS trial group.
- 22 Tremlett H, Paty D, Devonshire V. The natural history of primary progressive MS in British Columbia, Canada. *Neurology*. 2005;65(12):1919–23.
- 23 Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain*. 2006;129(pt 3):606–16.
- 24 Confavreux C, Vukusic S. Accumulation of irreversible disability in multiple sclerosis: from epidemiology to treatment. *Clin Neurol Neurosurg*. 2006;108(3):327–32.
- 25 Lebrun C, Bensa C, Debouverie M, et al. Association between clinical conversion to multiple sclerosis in radiologically isolated syndrome and magnetic resonance imaging, cerebrospinal fluid, and visual evoked potential: follow-up of 70 patients. *Arch Neurol*. 2009;66:841–6.