What about autoantibodies against interferon-beta?

Interferon-beta (β-IFN) represents the first-line immunomodulatory treatment for patients with relapsing-remitting multiple sclerosis (MS). However, over the last decade increased awareness of autoantibodies against β-IFN has emerged. These may develop in a variable percentage of treated subjects (2–45%), depending on the β-IFN compound and the assay method, and impair the therapeutic efficacy of interferons [1]. Recent European guidelines recommend measurement of neutralizing antibodies to be performed in all patients at 12 and 24 months of therapy, in specialized laboratories with validated methods. Follow-up of titers is not judged necessary in subjects who remain negative during this period, but therapy with β-IFN should be discontinued in those with high titers [2]; however, controversies with North American experts exist [3].

In this context, two recent studies carried out in Scandinavia attempted to investigate the natural course and the impact of steroids on these autoantibodies. In order to determine spontaneous titers’ fluctuation over time, a Swedish group investigated, retrospectively, a cohort of 822 MS patients treated with the three commercially available β-IFN compounds, who benefited from at least two autoantibodies testing at one year interval or more. They chose a cutoff of 150 TRU/ml for biological relevancy [4]. Overall, 72% of patients did not show any titer variation between the assays. This percentage was even higher in subjects at the two extremes (i.e., 97% with no antibodies, 91% with very high titers), while those with moderate titers tended to fluctuate more often. This trend was not influenced by treatment duration, β-IFN type, or the length of sampling interval. Interestingly, a decrease over time in antibodies titers appeared more often than an increase. The study was somewhat limited by its selection bias, and the use of laboratory assays prevents direct comparisons with other studies [5]. Nevertheless, these results may further support the practice of discontinuing β-IFN administration in subjects with high titers, and suggest some usefulness of repeated measurements in patients in the “grey zone”.

A Danish team designed a non-randomized interventional trial to assess the usefulness of the co-administration of 500 mg of methylprednisolone orally (three days monthly, for 6 months) in subjects with positive autoantibodies (cutoff not clear) combined with an absent in vivo response to β-IFN (tested using a cytopathic effect assay) [6]. There were 35 patients in the treatment sample, and 38 controls (subjects that chose not to undergo steroid administration and...
were given glatirameracetate [29 patients], or discontinued immunomodulatory treatment). Both groups were relatively similar, except for a higher proportion of men in the treatment group. At a 6 month follow-up, 21% of patients treated with methylprednisolone, and 11% in the control group regained an in vivo response to β-IFN (p = 0.35); also the percentage of patients experiencing a relapse during the study period was not different (18% vs 26%, p = 0.56). The authors concluded that these results do not suggest any benefit of steroids co-administration in patients with positive autoantibodies titers; however, this does not formally exclude a possible effect if immunosuppressive treatment is given at an earlier time point. As partly acknowledged by the authors, this study appears underpowered. Furthermore, the lack of randomization and the different treatment regimens among the two groups (i.e., the use of glatirameracetate) are of concern. The editorial also points out that, to date, no solid evidence shows that the in vivo assessment used in this trial correlates with the clinical response [7]. In fact, a preliminary observation from New Jersey suggests that identification of patients at risk of developing antibodies against β-IFN is possible by screening for “binding” antibodies repetitively in the first 12 months of treatment. These seem to develop earlier than “neutralizing” antibodies, and administration of methylprednisolone at this early time appears beneficial [8].

The management of patients developing autoantibodies to β-IFN remains challenging. Switching between different β-IFN compounds does not appear to represent a valid solution, as antibodies’ cross-reactivity has been demonstrated, and strategies to remove autoantibodies (such as plasma exchange or IVIG), or various combinations with other immunosuppressive agents, do not have any clear evidence of efficacy [7]. While a change to glatirameracetate is commonly used in this setting, further investigations are clearly needed to identify the best strategy.

References

MCQ

1. Which of the following statements is correct regarding anisocoria?
A The wider pupil lateralizes the lesion.
B The smaller pupil lateralizes the lesion.
C The swing-flash-light test is very helpful to detect an effenter deficit.
D Increase of the pupils’ difference in darkness is characteristic of a Horner syndrome.
E Increase of the pupils’ difference in darkness is characteristic of a parasympathetic deficit.

2. Please indicate the wrong sentence:
A After a thorough analysis, most ictal headaches result in being benign.
B Hypnic headache may interfere with sleep.
C “SUNCT” is practically always unilateral.
D A “sentinel” headache may precede, by hours or days, catastrophic aneurysmal bleeding.
E A history of smoking does not correlate with the prevalence of cluster headaches.

3. Please indicate the correct statement related to the treatment of acute ischemic stroke:
A The time window for IV thrombolysis has been recently widened to 4.5 h because the efficacy remains constant over this time lapse.
B Before IV thrombolysis, arterial pressure should always be quickly lowered below 150/80 mm Hg with labetolol.
C After IV thrombolysis, it is better to wait 2–3 h before administering antiplatelet agents.
D “Malignant” ACM ischemia presents more often in elderly people.
E Considering the “odds ratios”, decompressive craniotomy represents the most efficacious treatment for survival after acute stroke.

4. Which of the following statements regarding status epilepticus (SE) is correct?
A Since most complex-partial seizures last for more than 4 minutes, it is premature to consider SE after 5 minutes.
B SE refractory to 2 treatment lines should always be treated with coma induction.
C The most common etiologies in adults are cerebrovascular diseases and drug withdrawal.
D The drug of choice for initial treatment is phenytoin, since it does not impair consciousness.
E The most important prognostic predictors are gender and ethnicity.
5. Which sentence is incorrect?
A  A patient with myasthenia gravis, complaining of acute shortness of breath, should be observed in a monitored unit.
B  Magnesium sulphate represents a suitable treatment for muscular discomfort in patients with myasthenia.
C  Patients with a Guillan-Barré syndrome may present with marked dysautonomic features.
D  Corticosteroids should not be used in acute Guillan-Barré syndrome.
E  Miller-Fisher syndrome and Bickerstaff encephalitis could be seen as a continuum entity.

Neuroimage answer

At the left fronto-polar region, one may notice that the cortical-subcortical differentiation appears less sharp than in other areas. Furthermore, the cortex seems thinner and more hyperintense. Finally, there is a halo of hyperintensity directing towards the frontal horn of the lateral ventricle. This “transmantle” signal of abnormality, which is somewhat better seen on the T1 image (below), is a classic finding in focal cortical dysplasia. These abnormalities are highly epileptogenic.

As a relatively rare but characteristic element, this patient describes an aura that may suggest a “forced thinking”, a feature that has been reported to occur with dominant epileptic foci (i.e., mostly left-sided). After the carbamazepine dose was increased to 1000 mg per day, he remained seizure-free (more than one year follow-up).

Figure 2
T1 axial MRI.

MCQ Answer key:
1. D
2. E
3. E
4. C
5. B