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JOURNAL CLUB

Multiple sclerosis II: new diagnostic criteria, association with smoking and effects of cannabis on cognitive function

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Very recently a clinically highly relevant rapid communication was published in Annals of Neurology on new diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald Criteria. Therefore, the first article presented in this month's Journal Club will focus on this important issue. The new criteria are evidently easier to apply, in particular the imaging criteria that are becoming more and more important nowadays. The second article is on the relevance of smoking and its interaction with two human leukocyte antigens for increased risk of multiple sclerosis. The accompanying editorial seems to be even more interesting than the primary article. The third and final article shows that despite the benefit of "street cannabis" on pain and spasticity relief, the associated cognitive side effects should be taken seriously.

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

As R.A. Rudick from Cleveland nicely summarizes in the accompanying editorial to this article, the different diagnostic criteria for multiple sclerosis which have been proposed over the last 45 years are discussed. The Schumacher criteria, published in 1965 emphasized the concept of disease disseminated in time and space. The diagnostic criteria of Poser and colleagues, published in 1983 in Annals of Neurology, incorporated for the first time non-clinical testing without, of course, MRI criteria. The initial version of the McDonald criteria was published in 2001 and a revision was published in 2005 (all in Annals of Neurology). Their use in the clinic was, however, complex and difficult. Even experienced specialists were uncertain about some aspects of the criteria (for references, see Rudick 2011). In the current issue of Annals of Neurology, Polman from Amsterdam and the other members of the International Panel on the Diagnosis of Multiple Sclerosis now present the 2010 version of the McDonald criteria. They have, in particular, focused on requirements for demonstrating dissemination in space and in time. They also pointed out as Schumacher did in 1965 that it remains imperative that alternative diagnoses are considered and excluded. Another issue was the often difficult differential diagnosis for multiple sclerosis of neuromyelitis optica and the neuromyelitis optica spectrum disorders. Further issues were primary progressive multiple sclerosis, pediatric multiple sclerosis, and multiple sclerosis in Asian and Latin–American populations. In Tables 1, 2, 3, 4 you will find the 2010 McDonald criteria for demonstration of dissemination in space, dissemination in time, as well as the 2010 criteria for diagnosis of multiple sclerosis and primary progressive multiple sclerosis.

Magnetic resonance imaging criteria for dissemination in space (see Table 1): according to the current criteria this can be demonstrated with at least one T2 lesion in at least two of four locations considered characteristic for MS: juxtacortical, periventricular, infratentorial, and spinal cord.

These recommendations, as well as those that will follow, are based on the simplified MRI criteria developed by Swanton and co-workers in 2006 and 2007 (for references, see Polman et al. 2011). Magnetic resonance imaging criteria for dissemination in time (see Table 2): either a new T2 and/or gadolinium-enhancing lesion on follow-up MRI

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Table 1 MRI diagnostic criteria for dissemination in space, based on Swanton et al (2006, 2007)

Dissemination in space can be demonstrated by at least 1 T2 lesion[a] in at least two of four areas of the CNS
Periventricular
Juxtacortical
Infratentorial
Spinal cord[b]

[a] Gadolinium enhancement of lesions is not required for dissemination in space

[b] If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count. From Polman et al. (2011)

Table 2 MRI diagnostic criteria for dissemination in time, based on Montalban et al. (2010)

Dissemination in time can be demonstrated by
1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
2. Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time

From Polman et al. (2011)

or the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time.

Cerebrospinal fluid findings: positive CSF findings, i.e., elevated immunoglobulin G index or two or more oligoclonal bands are still important to support the inflammatory nature. In contrast to the 2005 criteria, this does not change the MRI requirements. The criteria for diagnosis of primary progressive multiple sclerosis are summarized in Table 3.

At the end of the article the authors point out that we still do not have any specific biomarkers to confirm the diagnosis. Increased immunoglobulin G index or the presence of oligoclonal bands in the CSF simply support an MS diagnosis and aquaporin-4 antibodies can help in the differential diagnosis. In Table 4 all the criteria are summarized.

Conclusions and comments

The 2010 update of the diagnostic McDonald criteria for multiple sclerosis is a major advance, particularly since the MRI criteria have been simplified. Therefore, their daily use will be much easier. The new criteria should be considered the standard from now on, not only for clinical routine but also for clinical studies. Final remark: the long list of potential conflicts of interest of the authors—almost 1½ pages—shows how research in this field is generously supported by pharmaceutical companies with its pros and cons.

Table 3 Diagnostic criteria for primary progressive multiple sclerosis (from Polman et al. 2011)

Primary progressive multiple sclerosis may be diagnosed in subjects with
1. 1 year of disease progression (retrospectively or prospectively determined)
2. Plus 2 of the 3 following criteria[a]
A. Evidence for DIS in the brain based on _1 T2[b] lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)
B. Evidence for DIS in the spinal cord based on _2 T2[b] lesions in the cord
C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

[a] If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the criteria

[b] Gadolinium enhancement of lesions is not required

Polman CH et al (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69:292–302

Rudick RA (2011) Diagnostic criteria for multiple sclerosis: headed in the right direction but still ways to go. Ann Neurol 69:234–236

Smoking and two human leukocyte antigen genes interact to increase the risk for multiple sclerosis

Basically this is an interesting study, but the accompanying editorial/scientific commentary by S. Sawcer and G. Hellenthal of Cambridge and Oxford, which is provided with a very careful statistical analysis and description of regression analysis, seems to be even more interesting. This is particularly true for two statements. "… it is important to remember that statistical analysis only allows us to judge whether an observed difference exceeds that expected by chance. It does not of itself show that the tested exposure is relevant to the pathogenesis, nor that it is correlated with something of relevance to it, unless we can be sure that other potential causes for the observed difference have been avoided." Furthermore, in relation to the study on smoking and the risk for multiple sclerosis, the final sentence of the editorial/scientific commentary: "But regardless of interpretation, the medical advice is clear: 'don't smoke, it's bad for you'." After reading this, you might stop reading the summary of "Smoking and two human leukocyte antigen genes interact to increase the risk for multiple sclerosis" or you might continue to get more details.

Table 4 Summary of the current diagnostic criteria for multiple sclerosis

Clinical presentation	Additional data needed for MS diagnosis
Two or more attacks[a]; objective clinical evidence of two or more lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack[b]	None[c]
Two or more attacks[a];	Dissemination in space (see Table 1)
One attack[a]; objective clinical evidence of two or more lesions	Dissemination in time (see Table 2)
One attack[a]; objective clinical evidence of one lesion (clinically isolated syndrome)	Dissemination in space and time (see Tables 1, 2)
Insidious neurological progression suggestive of MS (PPMS)	See Table 3

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is ''MS''; if suspicious, but the Criteria are not completely met, the diagnosis is ''possible MS''; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is ''not MS''

[a] An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 h, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 h. Before a definite diagnosis of MS can be made, at least one attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms

[b] Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least one attack, however, must be supported by objective findings

[c] No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS

(Modified from Polman et al. 2011)

There is good evidence that the pathogenesis of MS is related to environmental, genetic, and infectious factors. The familial aggregation supports the genetic factors. In particular genes of the human leukocyte antigen (HLA) complex seem to be relevant. For instance, the haplotype containing the HLA-DRB1*15 allele is associated with an increased risk for MS (odds ratio 2–4; for references, see Hedström et al. 2011). Smoking has been proposed to be an environmental factor in several epidemiological studies since 1961. In the current study Anna Karin Hedström from Stockholm and co-workers evaluated the potential interaction between smoking and the HLA-DRB1*15 and HLA-A*02 alleles, because these alleles modify the risk for MS (for references, see Hedström et al. 2011).

In a population-based, case–control study the authors included 843 cases of MS and 1209 controls. Both groups were classified by their smoking status as well as by HLA-DRB1 and HLA-A genotypes.

The major findings of this study were as follows. The authors found a significant interaction between two genetic factors, i.e., carriage of HLA-DRB1*15 and the absence of HLA-A*02 in smokers only. There was no such interaction in non-smokers. Statistical analysis revealed that the odds ratio was 13.5 for smokers with both genetic risk factors. The odds ratio for smokers without genetic risk was 1.4. The odds ratio for non-smokers with both genetic risk factors was 4.9. Taken together, smoking increased the risk for MS by a factor of 2.4 in those with both genetic factors vs 1.4 in those without genetic risk factors.

Conclusions and comments

The authors concluded that their findings are consistent with the hypothesis that priming of the immune response in the lungs may substantially lead to MS in genetically susceptible persons. Sawcer and Hellenthal comment on this conclusion in the accompanying editorial: "In summary, it is very hard to perform reliable association studies assessing genetic factors, but it is even harder to perform such studies for environmental exposures, where vulnerability to confounding is increased and measurement is inherently less precise." Further: "Great care must be taken to distinguish statistical from biological interaction."

In the end it is hard to decide what we really learn from this study, except that smoking is not beneficial to your health. And this message does not depend on your HLA genotypes. In other words, the conclusion for clinical practice and consulations with our patients and non-patients is straightforward.

Hedström AK et al (2011) Smoking and two human leukocyte antigen genes interact to increase the risk for multiple sclerosis. Brain 134:653–664
Sawcer S, Hellenthal G (2011) The major histocompatibility complex and multiple sclerosis: a smoking gun? Brain 134:638–640

Effects of "street cannabis" on cognitive function in patients with multiple sclerosis

Some clinical studies show that cannabis in patients with multiple sclerosis (MS) has a beneficial effect on spasticity pain and bladder dysfunction. The effects of cannabis on cognition were examined in a double-blind, placebo-controlled, crossover study in patients with MS. These studies showed no association between cannabis and cognitive deficits (for references, see Honarmand et al. 2011). All these trials used synthetic, clean cannabis derivates. The effects on inhaled "street cannabis" have so far not been analyzed.

The current study by Hornamand and co-workers included 50 patients with MS; 25 were "street cannabis" users and 25 non-users. They underwent a minimal assessment of cognitive function: the Hospital Anxiety and Depression Scale as well as the Structured Clinical Interview for DSM.-IV Axis I Disorders. It is important to note that about 40–60% of patients with MS have cognitive dysfunction, which significantly impairs quality of life.

The major findings of this study were as follows. (1) "Street cannabis" users performed significantly less well than non-users on measures of information processing speed, working memory, executive functions, and visuospatial perception. (2) They were twice as often classified as globally, cognitively impaired. (3) There were no differences between the two groups in terms of depression, anxiety, or lifetime structural interview for the DSM-IV I psychiatric diagnosis. (4) The average age at onset of cannabis use was 17 years and the average duration of cannabis use was 26.6 years.

Conclusions and comments

This study clearly demonstrates that "street cannabis", which is most often inhaled, has significantly adverse effects on cognition following prolonged use. These results have to be replicated in a larger study. The discrepancy between this study and negative findings in previous studies can be explained by the effects of oral administration of cannabinoids: there is a slower onset of action, more erratic patterns of absorption, and lower peak concentration compared to that of inhaled cannabis.

What are the clinical consequences of this study? First, a detailed neuropsychological testing of patients with MS seems to be mandatory for future studies of cannabis. However, the subjective benefits that patients may derive from using "street cannabis" should be weighted against the associated cognitive side effects. This is most likely also true for the synthetic derivates of the drug taken orally.

Honarmand K et al (2011) Effects of cannabis on cognitive function in patients with multiple sclerosis. Neurology 76:1153–1160