Tabagisme et sclérose en plaques

Liège, 19 mars 2016

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What is Multiple Sclerosis?

a systemic dysregulation of the immune system leading to

an inflammatory disease of the CNS with focal lesions (adaptive > native immunity)

and at the same time, an inflammatory neurodegenerescence (native > adaptive immunity)
The lesions are restricted to the central nervous system

- the brain (white and gray matters)
- the optic nerves
- the brainstem
- the cerebellum
- the spinal cord
- the meninges (pia matter)
Blood vessel

1. Capture & rolling
2. Activation & adhesion
3. Migration

EC
CNS parenchyma

SLex
Selectin
LFA-1
ICAM-1
VLA-4
VCAM-1
BBB
Brain volume is not significantly reduced in patients with CIS (De Stefano, Arch Neurol 2002), but it shows an early progressive decline in those patients who later develop MS.

Δαλτον αλ, JNNPI, 2002, 73 : 141–147
Optimisation du traitement

- Poussées / Handicap
- Activité IRM
- IRM Charge lésionnelle
- Volume cérébral
- Perte axonale

Stabilité de la pathologie

Susceptibility biomarkers

In Caucasian populations, approximately 65% of MS patients carry the HLA-DRB1*1501 allele compared to 30% of healthy controls.
Susceptibility biomarkers

IMMUNOGENETICS and MULTIPLEX FAMILY

- the biggest “Multiplex family” studied so far \textit{(Dyment et al, 2008)}:

  82 members, including 14 MS patients

  HLA-DRB1* 15 present in 11 out 14 patients (79 %)

  in 38 % of non-MS members (p=0.005)
Susceptibility biomarkers

About 70 susceptibility genes (allelic variants) have been described in MS patients

- most of them are related to the immune system, not to neurodegeneration
- some are related to the metabolism of vitamin D
- some are common with other inflammatory diseases: rheumatoid arthritis, lupus erythematosus, psoriasis, Crohn’s disease, juvenile diabetes type I
Susceptibility biomarkers

IMMUNOGENETICS and TWIN STUDIES

Concordance always 4 to 5 times higher in monozygotic twins than in dizygotic twins.

Concordance in monozygotic twins depends on the prevalence of the disease in the areas where twins are living!

- 38% in Canada (Ebers, 2008)
- 14.5% in Italy (Ristoni et al, 2006)

Higher prevalence of the disease, in the overall population, higher concordance in monozygotic twins!

But this fairly low concordance rate indicates a role for environmental factors.
Non genetic markers of susceptibility

- viral infections
- low sun exposure and low vitamin D levels
- low uric acid levels
- high BMI, high salt intake?
- SMOKING
Figure 1. Risk factors in EnvIMS.OR of MS risk for risk factors reported in previous studies using EnvIMS data.
Susceptibility biomarkers

The sex ratio

- the worldwide prevalence of MS is increasing, but only in women! (from 1.0 to 1.2/1000 in Belgium)
- the birth year is predictive of the sex ratio of MS patients when the disease occurs

Only environmental factors may explain such a change in the sex ratio of MS patients
Female to male ratio of MS patients in Canada by year of birth, spanning a 50 year period (n : 27074) (Orton et al, 2006)
## Susceptibility biomarkers

<table>
<thead>
<tr>
<th>Disease</th>
<th>P value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumps</td>
<td>0.62</td>
<td>0.98</td>
<td>0.92-1.05</td>
</tr>
<tr>
<td>Mumps vaccine</td>
<td>0.02</td>
<td>1.09</td>
<td>1.01-1.17</td>
</tr>
<tr>
<td>Measles</td>
<td>0.47</td>
<td>0.97</td>
<td>0.91-1.05</td>
</tr>
<tr>
<td>Measles vaccine</td>
<td>0.04</td>
<td>1.08</td>
<td>1.00-1.16</td>
</tr>
<tr>
<td>Rubella</td>
<td>0.06</td>
<td>0.93</td>
<td>0.87-1.00</td>
</tr>
<tr>
<td>Rubella vaccine</td>
<td>0.03</td>
<td>1.09</td>
<td>1.00-1.17</td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>0.52</td>
<td>1.02</td>
<td>0.96-1.09</td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>0.07</td>
<td>0.92</td>
<td>0.84-1.01</td>
</tr>
<tr>
<td>Varicella</td>
<td>0.06</td>
<td>1.07</td>
<td>1.00-1.14</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>&lt;0.001</td>
<td>2.06</td>
<td>1.71-2.48</td>
</tr>
</tbody>
</table>

Age- and sex-adjusted p values and odds ratios on the risk of developing MS as assessed by logistic regression (14362 MS; 7671 partners)

*Ramagopalan et al, Neuroepidemiology, 2009; 32 : 257-262*
Low vitamin D level and risk for MS

- High levels of serum 25-hydroxyvitamin D (> 99 nmol/L), especially before age 20, are associated with a lower risk of MS (OR : 0.38; 95 % CI : 0.19-0.75; p = 0.006) (Munger et al, JAMA, 2006)

- Because food provides little vitamin D, the major source for most people is through skin exposure to sunlight. UV radiation is responsible for photolyzing 7-dehydrocholesterol to vitamin D3.

- There is a reduced risk associated with sun exposure, and use of vitamin D supplements (Nurses Health Study I and II; van der Mei et al, BMJ, 2003).
Estimates of the regional prevalence of MS on 1 January 2003, per 100.000 inhabitants, standardised by age, among French farmers (Vukusic et al, 2007)
August monthly mean ultraviolet irradiation and MS prevalence in France. Arrow indicates the Poitou-Charentes region of anomalously low MS prevalence (Ebers, 2007)
Risk factor for MS: low uric acid level

- low serum uric acid levels
  - uric acid is the major endogenous low molecular weight antioxidant is very effective against peroxynitrite-derived radical (toxicity in MS lesions)
  - the mean serum level of uric acid is lower in MS than in other neurological diseases
  - mono- and dizygotic twins with MS have significantly lower serum uric acid than healthy siblings
  - MS is 15 times less frequent in people with chronic hyperuricemia (gout) than in a normal population (Hooper et al, 1998)
Risk factor for MS: smoking

- Smoking is a risk factor for developing MS


Nurses Health Study I and II (121,700 and 116,671)

Relative incidence rate of 1.6 (1.2-2.1) for current smokers;
cumulative exposure increased the risk
Risk factor for MS: smoking

- **Smoking is a risk factor for developing MS**

  ever-smoked versus never-smoked: OR of 1.6 (1.0-2.4)
  heavy smokers (20-40 cig/day): OR=1.9 (1.2-3.2)

  Riise et al, Neurology 2003,61:1122-24 (RR 1.81; 1.1 to 2.9)

  Pekmezovic T et al, Neuroepidemiology, 2006,27:212-216
  OR=2.4, p=0.004
Risk factor for MS: smoking

- smoking is a risk factor for developing MS

« Tobacco smoking, but not Swedish snuff use, increases the risk of MS », Hedström AK et al, Neurology, 2009,73:696-701

A population-based case-control study in Sweden using incident cases of MS (902 cases, 1855 controls)
OR: 1.4 (1.2-1.7) for women; 1.8 (1.3-2.5) for men
The risk increased with increasing cumulative dose
Tabac à priser...

- **Définition:**
  - Le plus populaire de la gamme
  - Tabac humecté ou parfois sec, finement moulu en poudre vendu dans des boîtes en métal contenant une 20aine de sachets

- **Comment le consommer? 2 façons**
  - Malgré l’appellation, l’utilisateur renifle rarement ce produit ; il en place plutôt une pincée ou un sachet entre sa lèvre inférieure et sa gencive et laisse le tabac dans sa bouche sans mastiquer durant environ 30 min. on l’appelle aussi « trempage »
  - Celui qui le consomme par voie nasale en dépose une petite quantité sur le dos de la main fermée et aspire par une narine puis l’autre
Risk factor for MS: smoking

- Smoking is a risk factor for developing MS

“Smoking and Multiple Sclerosis susceptibility”, AK Hedström et al, Eur J Epidemiol, 2013, 28:867-874

Two Swedish population-based case-control studies (7883 cases and 9264 controls); ever smokers versus never smokers: OR at 1.5 (95% CI: 1.4-.6)

Clear dose response association between cumulative dose of smoking and MS risk (p value for trend <10^-35)
PASSIVE smoking is a risk factor for developing MS

Parental smoking at home and the risk of childhood-onset Multiple Sclerosis in children, Y. Mikaeloff et al, Brain, 2007, 130:2589-95

129 MS cases with onset < 16 y, 1038 controls

The adjusted Rate Ratio of a first episode of MS associated with exposure to parental smoking, was 2.12 (1.43-3.15). The RR increased with longer duration of exposure (2.49, 1.53-4.08)
PASSIVE smoking is a risk factor for developing MS

«Exposure to environmental tobacco smoke is associated with increased risk for Multiple Sclerosis», AK Hedström et al, MSJ, 2011, 17:788-793

695 MS cases, 1635 controls

The risk for MS was increased among never-smokers who had been exposed to passive smoking compared to never-smokers who had never been exposed (OR 1.3, 1.1-1.6)
Table 2. Odds ratio (OR) with 95% confidence interval (95% CI) of developing multiple sclerosis for subjects exposed to environmental tobacco smoke compared with those who have never been exposed, by duration of exposure.

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>Exposed cases</th>
<th>Exposed controls</th>
<th>OR (95% CI)*</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconditional (unmatched) analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>423</td>
<td>1094</td>
<td>1.0 (–)</td>
<td>1.0 (–)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>89</td>
<td>182</td>
<td>1.3 (1.0–1.8)</td>
<td>1.4 (1.0–2.0)</td>
</tr>
<tr>
<td>10–20</td>
<td>133</td>
<td>295</td>
<td>1.3 (1.0–1.7)</td>
<td>1.4 (1.0–1.8)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>50</td>
<td>84</td>
<td>1.8 (1.2–2.6)</td>
<td>1.8 (1.1–2.7)</td>
</tr>
<tr>
<td>Trend</td>
<td>–</td>
<td>–</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>Conditional (matched) analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>423</td>
<td>441</td>
<td>1.0 (–)</td>
<td>1.0 (*)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>89</td>
<td>76</td>
<td>1.4 (0.9–2.0)</td>
<td>1.6 (1.0–2.4)</td>
</tr>
<tr>
<td>10–20</td>
<td>133</td>
<td>124</td>
<td>1.3 (0.9–1.8)</td>
<td>1.3 (0.9–1.9)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>50</td>
<td>23</td>
<td>1.7 (1.0–2.8)</td>
<td>1.7 (1.0–2.9)</td>
</tr>
<tr>
<td>Trend</td>
<td>–</td>
<td>–</td>
<td>0.008</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, residential area, and ancestry.
†Adjusted for age, gender, residential area, ancestry, EBNA1 titres, a history of infectious mononucleosis, vitamin D status, UVR exposure habits, heredity, educational level, socioeconomic status, and body mass index.

AK Hedström et al. Mult Scler 2011;17:788-793
Smoking is a major preventable risk factor for MS

AK Hedström, T Olsson, L Alfredsson MSJ, 2015, in press

- 11% of the Swedish population were regular smokers in 2013, 17% reported to be exposed to passive smoke, 13% of infants born in 2010 had at least one parent who smoked.

- By comparison, 23% of the Belgian population are smokers, 26% in the range 26-34 years.
Smoking is a major preventable risk factor for MS

AK Hedström, T Olsson, L Alfredsson MSJ, 2015, in press

- a Swedish population-based case-control study (2455 cases, 5336 controls); the excess proportion of cases attributable to smoking and passive smoking was calculated as a percentage

- 20.4% of all cases were attributable to smoking or to passive smoking exposure. In subjects carrying the genetic risk factor HLA-DRB1*15 but lacking HLA-A*02, 41% of the cases were attributable to smoking
Smoking is a risk factor for early conversion to clinically definite Multiple Sclerosis after a first demyelinating event (called « clinically isolated syndrome or CIS »). The risk to develop a second relapse within 3 years after the first one was approximately two-fold higher among smokers compared with non-smokers.


Smoking is associated with increased lesion volumes and brain atrophy in Multiple Sclerosis.

Zivadinov R et al, Neurology, 2009, 73:504-510
Smoking and the course of MS

- Smoking worsens the prognosis in Multiple Sclerosis
  Sundström P and L Nyström, MSJ, 2008,14:1031-1035
  Ever smokers, especially with early smoking debut (<15 years of age) were more likely to have progressive disease compared with never smokers (p<0.01)

- Tobacco smoking and disability progression in Multiple Sclerosis: United Kingdom cohort study
  Manouchehrinia A et al, Brain, 2013,136:2298-2304
  Regular smoking is associated with more severe disease and faster disability progression
Risk factor for MS: smoking

- Smoking may promote MS progression via nitrogen oxide, a free radical linked to axonal damage in MS.

- Cigarette smoke contains high concentrations of free radicals with a potential neurotoxic effect (such as cyanide, and its metabolite, thiocyanate).

- Some components of the cigarette smoke could increase the blood-brain barrier permeability.

- Smoke exposure could induce pro-inflammatory immune responses via an increased production of IL-6 and IL-13.
Smoking beyond MS diagnosis
A risk factor still worth modifying

- quitting smoking appears to delay onset of secondary progressive MS and provide protective benefit

Ramanujam R. et al, JAMA Neurology, 2015, 1117-1123

Goldman MD and O. Stuve, Editorial, JAMA Neurology
Figure Legend:
Kaplan-Meier Plot of Quitters and Continuers A Kaplan-Meier plot with the age at conversion to secondary progressive (SP) disease for smokers at diagnosis who quit smoking completely (n = 118) and smokers at diagnosis who smoked continuously (n = 332).
Risk factor for MS: smoking

- Stopping smoking should be the first neuroprotective treatment in MS.

- Passive smoking should be avoided, especially for children of patients with MS, as they have a genetically increased risk (1 to 40, compared with 1 to 1000 in the general population).