Macrophagic myofasciitis

New insights on the long-term safety of aluminum adjuvants

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1. Macrophagic myofasciitis (MMF): A specific lesion in deltoid muscle
Macrophagic myofasciitis is an emerging condition characterized by specific lesions at muscle biopsy made of focal macrophagic infiltrates

Authier, 2007/06/25
2. MMF-associated Clinical Syndrome

Up to 17 alum shots (mean 5.2) in past 10yrs
Delayed clinical onset (mean 12mo) from last shot
Delayed muscle biopsy (mean 66 mo) from last shot

Myalgia (88%) + Chronic fatigue (87%) + Cognitive impairment (96%)
+ overt autoimmune disease (20%) : Multiple sclerosis (9%), DM, thyroiditis…

1. Significant association between myalgias and MMF: Gherardi et al, Brain 2001

2. Significant association between fatigue and MMF
   - case-control study: AFSSAPS, 2003
   - Total and Cognitive Fatigue scores (Impact Fatigue Scale) higher in MMF

3. Most MMF patients fulfill criterias for Chronic Fatigue Syndrome
   - Authier et al, Arthritis Rheum 2003
   - fatigue 93%, myalgias 87%, arthralgias 55%
   - CFS criteria (CDC/Oxford) 53%
3. MMF after anti-HPV immunization

8 girls referred to Henri Mondor hospital

- Age: at onset 15-18 yrs
  at evaluation : 16-23 yrs

- Deltoid muscle biopsy (7/8): normal: 5/7
  Macrophagic myofasciitis 2/7

<table>
<thead>
<tr>
<th>Vaccines:</th>
<th>GARDASIL 8/8</th>
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<tbody>
<tr>
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<td>REVAXIS (DTP) 3/8</td>
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<td>HBV 2/8</td>
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Patient #6

Experimental MMF lesion induced by i.m. injection of Gardasil
- C57.BL6 mouse
- 120 µl Gardasil i.m. in Tibialis anterior
- Sampling at D+28

![Biopsy images]
4. MMF is associated with Cognitive Dysfunction (MCI)

- quasi-constant (95%)
- stereotyped, dysexecutive type
- reported in workers exposed to inhaled Al

SPECT changes
non random & well-correlated

Associative posterior cortex
Itti & Authier (in préparation)

Verbal score
Flexibility
Inhibition
Planification
Perceptual Organisation
Verbal memory
Attention
Working Memory
Visual Memory

Joint dis. :
MMF:
(normalized values)

Comparison of profiles showed a significant difference in working memory and visual memory.

Authier, 2007/06/25
5. IM injection of alum-vaccine is followed by entry of Aluminum in brain

- Flarend et al (1997): rabbit, 26Al(OH)$_3$, IM
6. Neuromigration of alum particles is an active process

- Alum particles can be transported by monocyte-lineage cells to lymph nodes, blood and spleen, and, similarly to HIV, may use MCP1/CCL2-dependent mechanisms to penetrate the brain.

- This occurs at a very low rate in normal conditions explaining good overall tolerance of alum despite its strong neurotoxic potential.

- However, continuously escalating doses of the poorly biodegradable alum adjuvant in the population may become insidiously unsafe, especially in case of overimmunization
  - or immature/altered blood brain barrier
  - or high constitutive CCL-2 production.

*Khan et al. BMC Med 2013, 11, 99 (18 pages)*
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