Immunology of Pandemrix®-induced narcolepsy

**Background:** Narcolepsy type 1 is a chronic disorder causing disturbances in the regulation of sleep and wakefulness. The direct cause behind narcolepsy is a specific degeneration of hypocretin neurons. A strong genetic association to HLA allele DQB1*06:02 suggest an autoimmune explanation; specific autoantigens have so far not been identified. The incidence of narcolepsy increased following Influenza-vaccination with Pandemrix® in 2009/2010. The Pandemrix®-vaccine does not contain nucleoprotein from wild-type pandemic strain (NP CA2009) but nucleoprotein originating from Puerto Rico 1934 strain (NP1934).

**Methods:**
In vitro transcribed and translated 35S-methionine-labeled H1N1 influenza NPs as well as candidate autoantigens were expressed and used to determine presence of conformation-dependent (auto)antibodies. NP antibody affinities were determined using competitive assays with non-labeled NPs. HLA Class II HLA-DRB1, -DRB345, -DQA1, -DQB1, -DPA1 and -DPB1 were determined for 30 Pandemrix®-vaccine associated narcolepsy patients together with 64 First Degree Relatives.

**Aims:**
The aim for the project is to identify mechanism behind development of narcolepsy following vaccination;
1. Determine the antibody levels and affinity to NP1934 and NP2009. We test the hypothesis that levels and affinity of antibodies against the vaccine-containing nucleoprotein differ from wild type virus and may explain the adverse reaction to the vaccine.
2. Determine autoantibodies against narcolepsy candidate autoantigens; Alpha-Melanocyte-stimulating hormone, Tribbles homolog 2, Prepro-hypocretin, Hypocretin A, Hypocretin B, Hypocretin receptor 2 and ATP-sensitive inward rectifier potassium channel 10. We test the hypothesis that autoantibodies against candidate autoantigens are related to the immune response against the vaccine.
3. Determine whether genetic factors known to be associated with spontaneous narcolepsy are also associated to vaccine-induced narcolepsy. We test the hypothesis that co-inheritance of high risk HLA is more common among the affected family member.

**Preliminary results:** The project demonstrated increased NP antibody levels among childhood patients compared to age-matched controls. IgG antibody affinity towards vaccine NP1934 was lower for childhood patients, this while affinity towards wild-type NP2009 was comparable.

**Significance:**
The association between vaccination and narcolepsy may allow us to determine the mechanisms of disease development and the possible importance of components of the vaccine.
List of publications:


Not yet published, to be included in half-time thesis
ATP-Dependent Inwardly Rectifying Potassium Channel Kir4.1, Hypocretin 1, Hypocretin 2, PreproHypocretin, Preopiomelanocortin/ alpha-melanocyte-stimulating-hormone, tHypocretin receptor 2 and Tribbles Homolog 2 autoantibodies are absent in Pandemrix®-induced narcolepsy
Madeleine Wallenius, Omar Akel, Elin Arvidsson, Anita Ramelius, Carina Törn, Malin Fex, Lars Palm, Helena Elding-Larsson, Åke Lernmark, Alexander Lind

HLA Next Generation Sequencing in Pandemrix®-induced Narcolepsy
Lind Alexander, Akel Omar, Ramelius Anita, Kockum Ingrid, Lernmark Åke, Palm Lars, Larsson Elding Helena, Gerarghty Dan, Zhao Ping Lue

Not included in half-time thesis
