Hypocretin deficiency : neuronal loss and functional consequences

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Response to Intravenous Immunoglobulins and Placebo in a Patient with Narcolepsy with Cataplexy

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CHAPTER 5

Response to Intravenous Immunoglobulins and Placebo in a Patient with Narcolepsy with Cataplexy

Introduction

Narcolepsy with cataplexy is caused by a loss of hypocretin producing neurons in the lateral hypothalamus.[1,2] The strong Human Leukocyte Antigen (HLA DQB1*0602) association supports an autoimmune aetiology.[3] Still, there is no direct evidence for anti-neuronal antibodies or T-cell mediated autoimmunity to support this hypothesis.[4,5] Treatment with high-dose prednisone after acute onset of hypocretin-deficiency in an 8-year-old boy without cataplexy was not effective.[6] However, two studies suggested that treating narcoleptics with intravenous immunoglobulins (IVIg) shortly after disease onset may dramatically reduce the frequency and severity of cataplexy.[7,8]

Methods

We present a n=1 study in a 55 year old female patient suffering from typical narcolepsy with cataplexy for 7 years, who was almost unresponsive to any regular treatment, but had a dramatic response on open label treatment with IVIg. Polysomnographic findings were typical of narcolepsy with cataplexy. She was HLADQB1*0602 positive, hypocretin deficient and used venlafaxine (75 mg/day) with limited effects. Cataplexy was frequent and disabling (according to her diary: mean ± standard deviation; 3.30±0.15 complete attacks per day; range 3-4). Together with her severe excessive daytime sleepiness, the patient was invalided with profound impact on quality of life. She was almost homebound and evaded social activities to avoid a provocation of her complaints. After informed consent, we treated her with open label IVIg (1gm/kg/day over 2 days). After treatment she reported a clear reduction of cataplectic attacks and several days without any attacks. This effect lasted three weeks and disappeared gradually. Repeated treatment six months later showed a similar response. We started a double-blind placebo-controlled n=1 trial to analyse this remarkable response.[9]

This consisted of four successive treatment periods in which IVIg (1gm/kg/day over 2 days) or placebo was randomly administered.[9] The patient could request the 'rescue' medication for that period, if she did not experience significant clinical improvement within 10 days after treatment. This rescue medication was IVIg when the treatment

period was started with placebo and placebo when the treatment period was started with IVIg. The next treatment period was started after the patient indicated that the treatment effect had disappeared, and at least 4 weeks after the previous treatment. During the entire study period the patient kept a diary in which she noted the number of complete cataplectic attacks. Venlafaxine was continued in an unchanged dose throughout the entire study. Differences between the placebo and the IVIg periods were analysed using t-tests, corrected for the number of days within each period.

Results

The study lasted for 188 days. The patient correctly identified placebo and/or IVIg treatment in half (50%) of the treatment periods: the second (IVIg, 63 days) and third (placebo, 65 days). She mistook placebo for IVIg in the first treatment period (26 days) and IVIg for placebo in the fourth treatment period (34 days). During the preceding two month long baseline situation 1.45±2.72 complete cataplectic attacks per day were scored. During the study period both treatments resulted in a decrease of cataplectic attacks. IVIg treatment decreased the attack rate to 0.27±0.73 per day, and placebo to 0.48±1.28 attacks per day. The reduction of attacks of both treatments was significantly lower compared to the pre-study period ($p<0.001$ for both IVIg and placebo.). There was, however, no significant difference between the two treatment modalities ($p=0.17$).

Discussion

In conclusion, open treatment with IVIg led to a striking improvement in the frequency of the cataplectic attacks in this patient. However, during a subsequent double-blind

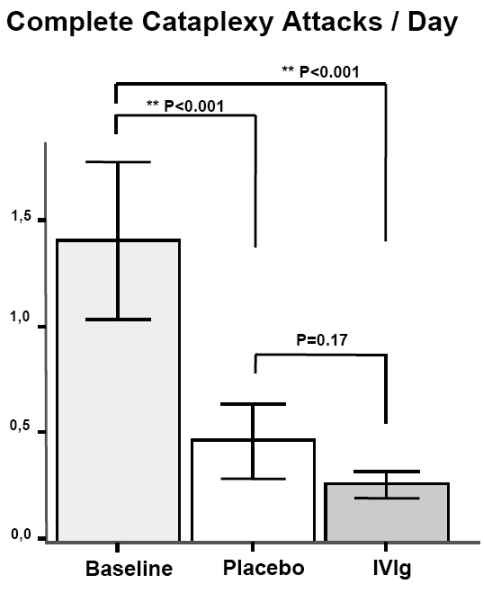

Figure 5.1
Cataplexy attacks / Day
Total number of cataplectic attacks for both treatment modalities and the baseline period. Error bars represent standard error of the mean. Differences were analysed using t-tests.

placebo-controlled n=1 trial there was no difference between placebo and IVIg treatment. Nevertheless, the placebo effect was impressive. The patient reported less cataplectic attacks after the first drug administration of the study, which was placebo. Carry-over effects of earlier received IVIg during the trial are thus unlikely. Earlier open studies found a decrease of cataplectic attacks around disease onset during IVIg treatment.[7,8] Although our patient did not receive IVIg near disease onset, there is no clear reason why there would be difference in placebo response between our case and the cases that were published earlier. Our findings stress the need for a large, double-blind placebo controlled study.

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