SHORT INVITED LECTURES – ABSTRACTS
KRATKA VABLJENA PREDAVANJA – POVZETKI

RIVASTIGMINE TREATMENT IN HUNTINGTON'S DISEASE – COMPARISON OF CLINICAL RESPONSE AND GENE EXPRESSION BIOMARKERS

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Background *Huntington's disease (HD) is a late-onset neurodegenerative disorder, inherited in an autosomal dominant manner. The disease manifests at a mean age of 35 years and is fatal after 15–20 years of progressive neurodegeneration. To date, no effective treatment to cure the disease or to slow its progression has been found. Currently, the therapy is only symptomatic, concentered on helping to handle some of the symptoms. On the other hand, use of cholinesterase inhibitor rivastigmine has shown some minor improvements in cognitive and motor functions in HD patients.[1–3] Unfortunatelly, after the onset of HD when disease progression is relatively slow, clinical rating scales like the Unified Huntington's Disease Rating Scale (UHDRS) and Total Functional Capacity (TFC), have high measurement variability.[4] Thus, both scales are insensitive to progression over short periods of time. Moreover, the scales have limited ability to distinguish effects on disease progression from symptomatic benefit. In addition, HD patients present with variable clinical phenotypes and this makes direct comparative assessments using clinical scales difficult. Therefore, there is a demanding need for validated biomarkers that may facilitate an accurate evaluation of the effectiveness of new therapies and improve the safety and efficiency of clinical trials. Global gene expression changes in blood of HD patients were already shown to exist and their potential as biomarkers was suggested.[5] A double-blinded clinical study was proposed to assess potencial beneficial clinical effect of rivastigmine for HD patients and suitability of gene candidates for monitoring the response to treatment.*

Methods *All patients were rated according to the UHDRS by two independent neurologists before the application of rivastigmine/placebo and 1 and 6 months later. Blood samples were taken at the same time points. 18 HD patients were included, 12 were given rivastigmine and 6 placebo. At the beginning rivastigmine was given 2 times daily in a dose of 1,5mg and after one month the dose was increased to 3mg 2 times daily. The control group was given placebo in the same capsules as the active substance. Laboratory protocols for RNA isolation and gene expression analysis were described elsewhere.[5] There were 2 dropouts in the clinical study – 1 patient died of acute pancreatitis and 1 patient decided to stop his participation after few weeks of treatment.*

Results *In the group of patients that were treated with rivastigmine, 7 out of 11 (63.6 %) patients after one month and 8 out of 11 (72.7 %) after six months showed improvement on UHDRS motor score. In the group of patients that were receiving placebo 2 out of 5 (40 %) patients after one month and 4 out of 5 (80 %) patients after six months showed improvement on UHDRS motor scores. No significant change was observed between both groups. When analysing gene expression, 9 out of 11 HD patients showed lower expression of candidate set after one month of treatment with rivastigmine and 7 out of these 9 HD patients still showed lower expression of candidate set after 6 months of treatment. The changes reached statistically significant difference in 5 out of 11 patients at both time points. In the placebo group not a single patient showed statistically significant lower ex-*

pression of candidate set at both time points. When analysing expression of each gene separately, all 12 genes were downregulated in the group treated with rivastigmine at both time points, although the changes did not reach statistical significance. In the group of patients that were receiving placebo there were minor changes in the expression of the 12 genes. After 1 month the expression was upregulated for all 12 genes and after 6 months there was no change in expression of 6 genes and minor up- or downregulation of other 6 genes. None of the changes reached statistical significance.

Discussion

Our results suggest that gene expression changes may be useful as an instrument in treatment response monitoring. When comparing gene expression in patients before treatment with rivastigmine and 1 and 6 months later we have shown that expression of limited number of preselected genes have not only changed but have also changed in an opposite direction as before treatment for some patients. Since clinical symptoms in HD change relatively slowly, more time is needed to correlate gene expression changes with clinical outcome, but we clearly showed a potential of expression profiles in blood as a surrogate markers.

References

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