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**An assessment of biomarkers importance in the cerebrospinal fluid to anticipate progression of subjective cognitive decline and mild cognitive impairment up to Alzheimer's-type dementia.**

**ABSTRACT**

**Introduction:**

Alzheimer's disease (AD) is one of the most frequent contemporary reasons of memory disorders among elderly people.

The general opinion is that the sequence of pathophysiological changes in the Alzheimer process (extracellular aggregation of  $\beta$ -amyloid plaques and neurofibrillary degeneration caused by intracellular concentration of hyperphosphorylated tau protein ) starts many years if not decades before full symptoms of the disease manifest themselves. The continuum of events, leading to the development of the full-blown picture of AD is of key importance. This awareness is a starting point for dividing AD as a disease into several stages: the pre-clinical stage of the disease i.e. subjective cognitive decline (SCD), mild cognitive impairment (MCI) and the actual dementia.

In order to identify patients at the pre-clinical stages of Alzheimer's disease i.e. SCD and MCI, it is imperative to mark biological indicators of the early Alzheimer's pathophysiological process. The analysis of the CSF biomarkers concentration (a lowered level of the  $\beta$ -amyloid ( $A\beta$ ) and a higher levels of the total tau protein (t-tau) and phosphorylated tau protein (p-tau)) is one of the methods.

Numerous data carried out to date have confirmed that patients without dementia with lower levels of A $\beta$  in the cerebrospinal fluid and higher levels of t-tau and p-tau, represent a high risk group in the development of Alzheimer's disease dementia.

**The aim of the study:**

The major assumptions underlying this work is the evaluation of the CSF biomarkers concentration depending on the severity of cognitive disorders with special emphasis placed on patients with progressive cognitive deficits.

What is more, this report contains analysis of CSF biomarkers concentration with Erlangen Score Algorithm which allows simple and quick interpretation of the results and a risk assessment of dementia development in the course of AD in patients with SCD and MCI.

**The Material and Methods:**

217 patients were recruited in the Neurology Clinic of the Central Clinical Hospital in Warsaw, Poland. Within two days of hospitalization, physicians conducted clinical interviews focusing on cognitive symptoms, coupled with physical, neurological and psychiatric examinations with special emphasis on cognitive disorders. Screening cognitive tests (Mini-Mental State Examination (MMSE) and neuropsychological evaluation were performed.

The patients from the analysed population were divided into three groups based on the clinical diagnosis. In this population, 31 were SCD subjects, 104 were diagnosed with MCI and 82 were patients with AD dementia.

CSF was obtained by means of a lumbar puncture. A $\beta_{1-42}$ , t-tau and p-tau concentrations were measured by using a sandwich enzyme-linked immunosorbent assay kit (ELISA) (Innogenetics, Gent, Belgium) in the hospital laboratory.

The further observation consisted of ambulatory visits with neurological and neuropsychological evaluation.

### **Results:**

We observed a significant main effect of the diagnosis on all of the CSF biomarkers.

The patients with more severe cognitive impairments had significantly lower level of  $A\beta_{1-42}$  amyloid and significantly higher level of the t-tau and p-tau proteins.

The SCD group had higher level of  $A\beta_{1-42}$  and lower level of the t-tau and p-tau proteins than those in the MCI group and those in the AD group. The MCI group had higher level of  $A\beta_{1-42}$  and lower level of the t-tau and p-tau proteins than patients in the AD group.

The  $A\beta_{1-42}/p$ -tau ratio was the strongest parameter of differentiating the analyzed groups.

The average clinical follow-up was 14 months ( $SD=6.82$ ). Progression of cognitive impairment was detected in the course of repeated neurological and neuropsychological evaluations in case of 16 subjects from the group with SCD and MCI ( $n=135$ ).

Patients who remained stable (SCD/MCI-S) had significantly higher level of  $A\beta_{1-42}$  and significantly lower level of the t-tau and p-tau proteins compared with patients with a progression (SCD/MCI-P) of cognitive impairment as well as patients with initial AD diagnosis. There was no difference between the participants with progression of cognitive impairment (SCD/MCI-P) and patients with initially diagnosed AD .

The  $A\beta_{1-42}/p$ -tau ratio was the strongest parameter differentiating the SCD/MCI-S group from the SCD/MCI-P group.

Furthermore, this research has shown that an analysis of the concentrations of the CSF biomarkers by using the Erlangen Score Algorithm allows determining the likelihood of developing Alzheimer's disease in patients presenting SCD and MCI. The higher the score, the bigger the risk of progression of cognitive impairment.

**Conclusions:**

Some patients with cognitive disorders at the MCI or even SCD stage represent a group with prodromal dementia in the course of Alzheimer's disease and analysis of CSF biomarkers concentration ( $A\beta_{1-42}$ , t-tau and p-tau) allowed to identify them.

Those patients, without dementia, with lower levels of  $A\beta_{1-42}$  and higher levels of t-tau and p-tau in CSF, represent a high risk group in the development of full-blown Alzheimer's disease.

Therefore, an analysis of the concentrations of CSF biomarkers by using the Erlangen Score Algorithm allows determining the likelihood of developing Alzheimer's disease in patients presenting SCD and MCI.

The group of patients, without progression during the period of observation, require continued follow up, especially those with pathological level of CSF biomarkers and Erlangen Score Algorithm 3-4, because there is a high risk of AD dementia development.