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The Erlangen Score Algorithm in the diagnosis and prediction of the progression from subjective cognitive decline and mild cognitive impairment to Alzheimer-type dementia

Anna Filipek-Gliszczyńska[1], Anna Barczak[2], Magdalena Budziszewska[3], Monika Mandecka[2], Tomasz Gabryelewicz[2], Maria Barcikowska[2]

[1]Neurology Clinic MSWiA Hospital, Warsaw, [2]Department of Neurodegenerative Disorders, Mossakowski Medical Research Centre, Polish Academy of Science, Warsaw, [3]Faculty of Psychology, University of Warsaw, Warsaw, Poland

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Abstract

The evaluation of cerebrospinal fluid (CSF) biomarkers for Alzheimer's disease (AD) (β-amyloid, t-tau, p-tau) can be used to estimate the risk of developing dementia in patients at the pre-clinical stages of AD, i.e. subjective cognitive decline (SCD) and mild cognitive impairment (MCI). Erlangen Score Algorithm allows interpretation of CSF biomarker concentrations and is cut-off value independent. The aim of this study was to establish if this algorithm can be applied for routine diagnostic testing in clinical and preclinical subjects and has prognostic value. We analysed 217 patients from the memory clinic with the diagnosis of SCD (n = 31), MCI (n = 104), and AD (n = 82) with clinical follow-up amounting to 14.33 months (SD = 6.82). It was found that the highest Erlangen Score dominated in the AD group and was the rarest in the SCD group. In the group of patients with progression of symptoms during our period of observation, the AD pathology was confirmed in 93.75% of cases. Among the non-progressing subjects (n = 119) the algorithm indicated the risk of developing AD as possible in 40.34% and probable in 15.97% of cases. To conclude, the Erlangen Score Algorithm is a useful tool to determinate the risk of developing AD before the onset of dementia or to confirm the AD diagnosis. It is extremely valuable in preclinical stages of AD for planning purposes and early intervention as well as for future clinical trials.

Key words: *Alzheimer's disease, mild cognitive impairment, subjective cognitive decline, cerebrospinal fluid biomarkers, Erlangen Score Algorithm.*

Introduction

The sequence of pathophysiological changes in the Alzheimer's process (extracellular aggregation of β-amyloid plaques and neurofibrillary degeneration caused by the intracellular concentration of hyperphosphorylated tau protein) starts many years before the full symptoms of the disease manifest themselves [6,22]. The $A\beta_{1-42}$ peptide is especially the one most prone to an aggregation resulting in amyloid plaques, which are a neuropathological hallmark of Alzheimer's disease (AD), along with the formation of neurofibrillary tangles (NFTs) [17]. The continuum of events leading to the develop-

Communicating author

Anna Filipek-Gliszczyńska, Neurology Clinic MSWiA Hospital, 137 Wołoska St., 02-507 Warsaw, Poland, e-mail: afilipekg@gmail.com

ment of the full-blown manifestation of AD is of key importance, and it 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 stage.

Subjective cognitive decline is characterised by the presence of subjective complaints on cognitive worsening, but which are not detected in objective evaluation, even in the neuropsychological assessment. Patients with MCI also report problems with cognition, but in this case the worsening is noticeable by informants and confirmed in neuropsychological assessment. Nevertheless, those patients remain independent in complex daily activities. More pronounced cognitive worsening along with the presence of problems in conducting everyday tasks are hallmarks of dementia. The presence of complaints of cognitive difficulties, regardless of their objectiveness, differentiate those stages of AD from normal controls. To identify patients at the pre-clinical stages of Alzheimer's disease, i.e. SCD and MCI, it is crucial to mark biological indicators of the earliest pathophysiological process of Alzheimer's disease.

The literature presents a great deal of evidence that patients with AD tend to have lower $A\beta_{1-42}$ values and higher t-tau (total tau) and p-tau (tau phosphorylated at threonine 181) proteins in the cerebrospinal fluid (CSF) tests [3,20,21,31].

The evaluation of lowered levels of $A\beta_{1-42}$ tends to display sensitivity of 86% and specificity of 89% in patients with AD against the healthy population. The evaluation of t-tau in CSF reveals a sensitivity of 80% and specificity of 89% in differentiating Alzheimer's disease with respect to controls [8]. The level of p-tau in CSF reflects the pathological process of neurofibrillary degeneration. The sensitivity of this biomarker for differentiating patients with AD and the healthy population amounts to 74% and specificity 92% [8]. A high level of p-tau in the CSF seems to be diagnosed only in patients with Alzheimer's disease in comparison to the other dementia syndromes [10,23,27,31,32,33,] or an acute period of stroke [10].

The coexistence of biomarkers of β-amyloid concentration and neurofibrillary degeneration is crucial to increase the degree of certainty in diagnosing Alzheimer's disease. The tau/$A\beta_{1-42}$ ratio has a sensitivity of 89% and specificity of 90% [2]. The assessment of the ratio between p-tau and $A\beta_{1-42}$ increases sensitivity (86%) and specificity (97%) of identification in relation to the healthy population as well as other types of dementia (sensitivity 80%; specificity 73%) [16]. Sensitivity and specificity of the tau/p-tau ratios amount to 96% and 100%, respectively [2].

Numerous tests carried out to date have confirmed that patients without dementia with lower levels of Aβ in the cerebrospinal fluid and higher levels of t-tau and p-tau represent a group at high risk of developing Alzheimer's disease dementia [4,18,19,21,26].

There is no simple pathognomonic biomarker for AD, and the overall analysis of CSF biomarkers (Aβ, t-tau, and p-tau) is valuable for diagnosis. The combination of existing biomarkers helps to differentiate the neurodegenerative processes; however, due to problems with each laboratory's specific norms, establishing the proper diagnosis could be challenging. Analysing only the raw concentrations of CSF is not sufficient for the diagnosis of the underlying pathology because existing discrepancies in protocols and storage of the CSF samples might result in a completely different outcome. Researchers suggest that a diagnosis-oriented interpretation of the CSF pattern is a better approach to support the diagnosis of AD [13].

The Erlangen Score Algorithm, proposed by Lewczuk *et al*. [13,15] seems to be a partial solution of those inter-centre discrepancies. It is an easy-to-implement algorithm to interpret CSF biomarkers concentration simultaneously. It can be applied for routine diagnostic testing and to facilitate the interpretation of the results because it enables us to categorise the CSF results into several categories, reflecting different degrees and patterns of pathological scores instead of the simple dichotomy of normal and abnormal results.

The Erlangen Score Algorithm is cut-off-value-independent and divides subjects into five categories from 0 to 4, in which 0 stands for the lack of the brain disease and 4 reflects probable AD.

See Table I for the interpretation details.

According to existing data, the Erlangen Score Algorithm is a useful tool to determinate the risk of developing AD before the onset of dementia or to confirm the AD diagnosis. The Erlangen Score Algorithm 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.

Table I. The interpretation of the Erlangen Score Algorithm

Score	Interpretation	Pattern of biomarkers
0	No evidence of organic CNS disease	Normal biomarkers
1	AD improbable	Slightly altered results of either Aβ or t-tau/p-tau, but not both
2	AD possible	Clearly pathologic results of either Aβ or t-tau/p-tau, but not both
2	AD possible	Slight alteration of both Aβ and t-tau/p-tau
3	AD possible	Clearly pathologic results of either Aβ or t-tau/p-tau accompanied by a slight alteration of the biomarker(s) of the other group
4	AD probable	All CSF AD biomarkers clearly pathologic

Table II. Participant characteristics for age, gender, and level of education in the three study groups

Variable	Whole sample	SCD	MCI	AD-dementia
n	217	31	104	82
Age	65.62 (9.84)	59.23 (7.68)	63.8 (9.23)	70.34 (9.25)
Gender, M/W	89/128	9/22	45/59	35/47
Level of education				
Primary school	34	1	14	19
Secondary school	92	14	46	32
University	91	16	44	31

Data is presented as mean (standard deviation)
M – men, W – women, SCD – subjective cognitive decline, MCI – mild cognitive impairment, AD – Alzheimer's disease

The aim of this paper was to establish whether the analysis of the concentration of the CSF biomarkers with Erlangen Score Algorithm in subjects with MCI and SCD is useful in diagnosing and predicting the clinical progression to dementia due to Alzheimer's disease.

Material and methods

Participants

A total of 217 patients (128 women and 89 men) were recruited between June 2011 and June 2014 in the Neurodegenerative Department of Neurology, Clinic of the Central Clinical Hospital in Warsaw, Poland. The study was approved by the Hospital Clinic's Ethics Committee. All subjects and/or their relatives gave their informed consent for the study.

The majority (58.9%) of the 217 study participants were women. The average age was 65.62 (SD = 9.84) years. Thirty-four participants completed primary schools only, 92 had secondary school diplomas, and 91 had university degrees. Participants were recruited from three groups according to the clinical diagnosis. In our study group, 31 persons were SCD subjects, 104 participants were diagnosed with MCI, and 82 were patients with AD dementia. The demographic characteristics are presented in Table II.

Within two days of hospitalisation, physicians conducted clinical interviews focusing on cognitive symptoms, coupled with physical, neurological, and psychiatric examinations with special emphasis on cognitive disorders. Screening cognitive tests and functional assessments were performed. Moreover, all the patients underwent neuropsychological evaluation. Furthermore, routine blood and brain imaging (magnetic resonance image [MRI] or computed tomography CT) were conducted. CSF from the lumbar puncture was obtained after all the above procedures.

The subjects were classified into three groups according to the clinical diagnosis. The patients with SCD (n = 31) were diagnosed according to Jessen *et al.*'s guidelines [12]. For MCI (n = 104) we used Petersen *et al.*'s criteria [29]. Dementia due to AD (n = 82) was established by means of the recent criteria adopted by the National Institute on Aging – Alzheimer's Association and the European Federation of Neurological Societies [1].

Patients aged below 45 years, with brain tumours, severe depressive syndrome, previous diagnosis of a major psychiatric disorder, history of alcohol or drug abuse, and other severe medical conditions that might be causes of cognitive impairments were excluded from the study.

The average clinical follow-up was 14.33 months (SD = 6.82). To assess the progression of cognitive impairment, all non-demented subjects (SCD/MCI, n = 135) were grouped together, and those who remained stable were described as SCD/MCI-S (n = 119), and participants whose results worsened were labelled as SCD/MCI-P (progressive, n = 16).

The second evaluation was based on neurological and neuropsychological assessments

Cerebrospinal fluid analysis

Six millilitres of CSF were obtained by means of a lumbar puncture with a non-traumatic spinal anaesthesia needle. After the lumbar puncture, only one patient reported a moderated headache. No other side-effects were registered. The CSF samples were centrifuged and stored in polypropylene tubes at –80°C. $A\beta_{1\text{-}42}$, 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 reference ranges were estimated in the hospital laboratory and were previously published elsewhere [17]. The cut-off values that were pathological for AD were as follows: $A\beta_{1\text{-}42}$ below 609.54 pg/ml, t-tau above 277.02 pg/ml, and p-tau higher than 55.08 pg/ml. To avoid a misdiagnosis in patients with the border scores, a 10% border zone was also implemented.

Results

Differences in the Alzheimer's disease biomarkers concentrations in the cerebrospinal fluid in the studied groups

To assess the differences between levels of AD biomarkers in CSF in all of the groups of patients we conducted one-way ANOVA. The results are shown in Table III.

We observed a significant main effect of diagnosis for all of the three biomarkers and two indexes. Patients with a more severe cognitive impairment had significantly lower levels of amyloid $A\beta_{1\text{-}42}$, $A\beta_{1\text{-}42}$/t-tau, $A\beta_{1\text{-}42}$/p-tau and significantly higher levels of the proteins t-tau and p-tau. $A\beta_{1\text{-}42}$/p-tau index accounted for the most pronounced differences between the groups.

The level of $A\beta_{1\text{-}42}$ differentiated participants in terms of diagnosis $F(2,214) = 36.29$; $p < 0.001$; $\eta^2 = 0.25$. The SCD group had higher levels of $A\beta_{1\text{-}42}$ than those in the MCI group (LSD test, MD = 147.19, $p = 0.006$) and in the AD-dementia group (LSD test, MD = 404.43, $p < 0.001$), and those in the MCI group had higher levels than did the AD-dementia group (LSD test, MD = 257.25, $p < 0.001$).

The level of t-tau differentiated participants in terms of diagnosis $F(2,214) = 35.63$; $p < 0.001$; $\eta^2 = 0.25$. The SCD group had lower levels of t-tau than those in the AD-dementia group (LSD test, MD = –326.75, $p < 0.001$), and those in the MCI group had lower levels than did the AD-dementia group (LSD test, MD = –288.16, $p < 0.001$). There were no significant differences for the remaining groups.

The level of p-tau differentiated participants in terms of diagnosis $F(2,214) = 21.01$; $p < 0.001$; $\eta^2 = 0.16$. The SCD group had lower levels of p-tau than those in the AD-dementia group (LSD test, MD = –32.89, $p < 0.001$), and those in the MCI group had statistically lower levels than did the AD-dementia group (LSD test, MD = –29.31, $p < 0.001$). There were no significant differences for the remaining groups.

The $A\beta_{1\text{-}42}$/t-tau ratio differentiated participants in terms of diagnosis $F(2,214) = 37.65$; $p < 0.001$; $\eta^2 = 0.26$. The SCD group had higher levels of $A\beta_{1\text{-}42}$/t-tau than those in the MCI group (LSD test, MD = 0.75, $p = 0.035$) and in the AD-dementia group (LSD test, MD = 2.62, $p < 0.001$), and those in the MCI group had higher levels than those in the AD-dementia group (LSD test, MD = 1.87, $p < 0.001$).

The $A\beta_{1\text{-}42}$/p-tau ratio differentiated participants in terms of diagnosis $F(2,214) = 42.85$; $p < 0.001$;

Table III. Differences in the Alzheimer's disease biomarker concentrations in the cerebrospinal fluid in different diagnosis statuses

	SCD	MCI	AD-dementia	ANOVA results		
	M (SD)	M (SD)	M (SD)	F	*p*	η^2
$A\beta_{1\text{-}42}$ (pg/ml)	817.05 (350.92)	669.87 (270.12)	412.62 (194.20)	36.29	< 0.001	0.25
t-tau (pg/ml)	277.61 (166.48)	316.20 (200.98)	604.36 (326.43)	35.63	< 0.001	0.25
p-tau (pg/ml)	46.77 (19.36)	50.35 (25.94)	79.66 (43.99)	21.01	< 0.001	0.16
$A\beta_{1\text{-}42}$/t-tau (pg/ml)	3.73 (2.01)	2.98 (1.94)	1.11 (1.28)	37.65	< 0.001	0.26
$A\beta_{1\text{-}42}$/p-tau (pg/ml)	19.88 (9.14)	16.36 (8.72)	7.09 6.41)	42.85	< 0.001	0.29

Data are presented as mean (standard deviation)
$A\beta_{1\text{-}42}$ – the CSF amyloid-Aβ-42(pg/ml), t-tau – the CSF total tau (pg/ml), p-tau – the CSF hyperphosphorylated tau (pg/ml), SCD – subjective cognitive decline, MCI – mild cognitive impairment, AD – Alzheimer's disease

η^2 = 0.29. The SCD group had higher levels of $A\beta_{1-42}$/p-tau than those in the MCI group (LSD test, MD = 3.52, p = 0.032) and in the AD-dementia group (LSD test, MD = 12.79, $p < 0.001$), and those in the MCI group had higher levels than those in the AD-dementia group (LSD test, MD = 9.27, $p < 0.001$).

Cerebrospinal fluid abnormal levels of biomarkers in the studied group

From the neurochemical perspective, the evaluation of biomarkers of Alzheimer's pathology in CSF in subjects with preclinical phases was helpful in the identification of persons who are particularly at the risk of developing dementia.

In patients with SCD, an abnormal, AD-specific level of $A\beta_{1-42}$ was found in 23.5% of patients, pathological levels of t-tau protein in were present in 31.8%, and p-tau protein in 21.2% of participants. However, the pathological values of $A\beta_{1-42}$/t-tau ratio were found in 20% of SCD patients, and $A\beta_{1-42}$/p-tau was present in 11% of them. It means that despite the absence of cognitive impairment in the neuropsychological assessment, individuals with subjective cognitive dysfunction present with typical AD pathology, expressed by abnormal concentrations of neurochemical markers.

As expected, almost half of the patients with MCI diagnosis from the studied group had pathological levels of $A\beta_{1-42}$ (44.8%), t-tau protein (43.7%), and p-tau protein (35.6%). In contrast, the values of $A\beta_{1-42}$/t-tau ratio typical for AD were found in 47.1% of patients with MCI and abnormal $A\beta_{1-42}$/p-tau ratio value was present in 39.1% of MCI subjects. It was also shown that in comparison to the SCD group, the abnormal concentrations of AD biomarkers were more than twice as common in the MCI group, which is related to the much greater degree of cognitive impairment revealed in the neuropsychological assessment.

In the demented group, abnormal levels of $A\beta_{1-42}$ were observed in 91.3% of subjects, t-tau protein levels in 83.8% of them, and p-tau proteins in 75%. Pathological values of $A\beta_{1-42}$/t-tau ratio were found in 87.5% of patients with dementia along with the abnormal values of $A\beta_{1-42}$/p-tau ratio in 86.3% of participants with dementia due to AD. The distribution of abnormal CSF biomarkers values in the described group is shown in Table IV.

Differences in the Erlangen Score in the studied groups

The CSF biomarkers were analysed with respect to the Erlangen Score Algorithm. It was found that in

Table IV. Distribution of abnormal cerebrospinal fluid biomarkers values in study participants

Variable	Whole sample (n = 217)	SCD (n = 31)	MCI (n = 104)	AD-dementia (n = 82)
$A\beta_{1-42} \leq 609.54$	131 (60.4%)	10 (32.3%)	47 (45.2%)	74 (90.2%)
t-tau ≥ 277.02	122 (56.2%)	10 (32.3%)	46 (44.2%)	66 (80.5%)
p-tau ≥ 55.08	99 (45.6%)	9 (29%)	31 (29.8%)	59 (72%)

SCD – subjective cognitive decline, MCI – mild cognitive impairment, AD – Alzheimer's disease, $A\beta_{1-42}$ – the CSF amyloid-Aβ-42 (pg/ml), t-tau – the CSF total tau (pg/ml), p-tau – the CSF hyperphosphorylated tau (pg/ml)

Table V. The Erlangen Algorithm scores in three study groups

The Erlangen Score	Risk of developing AD	Whole sample (n = 217)	SCD (n = 31)	MCI (n = 104)	AD-dementia (n = 82)
0	None	52 (24.0%)	15 (48.4%)	33 (31.7%)	4 (4.9%)
1	Improbable	6 (2.8%)	0	5 (4.8%)	1 (1.2%)
2-3	Possible	71 (32.7%)	13 (41.9%)	42 (40.4%)	16 (19.5%)
4	Probable	88 (40.6%)	3 (9.7%)	24 (23.1%)	61 (74.4%)
Underlying AD pathology (2,3 and 4 scores together)	Possible and probable	159 (73.3%)	16 (51.6%)	66 (63.5%)	77 (93.9%)

Data presented in number of patients (percentage)
SCD – subjective cognitive decline, MCI – mild cognitive impairment, AD – Alzheimer's disease

the group of the AD dementia patients, the result of the Erlangen Score Algorithm suggested an underlying AD pathology in 93.9% of the cases. In the MCI group, it amounted to 63.5% (in 23.1% of the participants defined as probable and in 40.4% as possible). Furthermore, in the SCD group, the Erlangen Score Algorithm results implied an underlying AD pathology in 51.6% of the cases (9.7% as probable and 41.9% as possible). See Table V for detailed data.

Erlangen Score in the follow-up analysis

We also analysed CSF biomarkers with respect to the Erlangen Score Algorithm after an average clinical follow-up of 14.33 months in subjects without dementia. Due to the relatively brief period of observation and small numbers of certain groups, progressive non-demented subjects (SCD/MCI-P) were analysed together. It transpired that in this progressive population (SCD/MCI-P) (n = 16) that 15 subjects scored two, three, or four points (93.75%), confirming the AD pathology. Among the non-progressing subjects (n = 119) only 56.31% scored two, three, or four points, determining the risk of developing AD as possible (40.34%) or probable (15.97%). The higher the score, the greater the risk of progression of cognitive impairment (χ^2 [3, n = 135] = 13.26; p = 0.004, where V Kramer = 0.31). Table VI presents Erlangen Algorithm Scores for groups of progressive and non-progressive subjects.

Discussion

The characteristic profile of the biomarkers in CSF appears early and is maintained in the course of the development of Alzheimer's disease [19]. According to the criteria, the typical configuration of AD biomarker in CSF confirms Alzheimer's disease as the reason behind cognitive disorders in patients with dementia [5,7,30]. The Erlangen Algorithm Scores ranging from 0 to 4 (Table I) enables not only the detection of the underlying pathology but also staging of the disease progression. Although the use of the Erlangen Algorithm Score is not worldwide, it seems to be a valuable tool for both diagnostics and prediction purposes. It also minimises the risk of misdiagnosis in clinically uncertain cases in patients with MCI and SCD. The differences between laboratories with respect to concentrations of the CSF biomarkers may occur from applying different techniques, reagents, methods of collecting and storing the cerebrospinal fluid, or statistical methods of evaluating the cut-off points for the subsequent parameters, specific to the laboratory [14]. The Erlangen Algorithm Score is cut-off-value-independent and can be easily adopted by laboratories irrespective of their analytical platform and the reference ranges. Therefore, it is suggested that the Erlangen Score Algorithm be implemented in the interpretation of the results, especially in situations when the subject provides the results from a facility with unknown laboratory norms.

The studied population (Table II) was divided into three groups (SCD, MCI, and AD-dementia) regarding their level of impairment based on the clinical evaluation. Obtained results from the CSF biomarkers analysis pointed to the differences in the levels of $A\beta_{1-42}$, t-tau, and p-tau along with the levels of $A\beta_{1-42}$/t-tau and $A\beta_{1-42}$/p-tau ratios with respect to the subject's diagnosis (Table III). It allowed the categorisation of the CSF results, reflecting different degrees and constellations of pathological findings.

In our paper, we analysed the concentration levels of the CSF biomarkers ($A\beta_{1-42}$; t-tau and p-tau) by means of the Erlangen Score Algorithm [15] in subjects with clinical diagnosis of SCD, MCI, and AD-

Table VI. The Erlangen Algorithm Scores in follow-up analysis

The Erlangen Score	Risk of developing AD	SCD/MCI (n = 135)	SCD/MCI-P (n = 16)	SCD/MCI-S (n = 119)
0	None	48 (35.56%)	1 (6.25%)	47 (39.49%)
1	Improbable	5 (3.70%)	0	5 (4.20%)
2-3	Possible	55 (40.74%)	7 (43.75%)	48 (40.34%)
4	Probable	27 (20.00%)	8 (50.00%)	19 (15.97%)
Underlying AD pathology 2, 3, and 4 scores together	Possible and probable	82 (60.74%)	15 (93.75%)	67 (56.31%)

Data presented in number of patients (percentage)
SCD – subjective cognitive decline, MCI – mild cognitive impairment, SCD/MCI-P – SCD/MCI progression, SCD/MCI-S – SCD/MCI stable

dementia. The obtained results were in line with the existing data [13,15], and in more advanced patients the highest Erlangen Score was the most common in AD subjects, but the rarest in the SCD subjects. On the other hand, half of the clinically normal SCD population in our study had possible and probable AD pathology, which makes this group more exposed for future risk of dementia development, despite the lack of any cognitive deficits observed in the detailed neuropsychological assessment. The MCI population was similar to the SCD subjects in terms of having a possible risk of AD, but the probable risk was increased, with a lower number of persons with no risk (Table IV). Because there are no published data of the Erlangen Score distribution in the non-demented population, our results are novel and those findings could shed some light on this area of research.

The utilisation of the Erlangen Algorithm Score enables for risk estimation of developing Alzheimer's-type dementia in patients with SCD and MCI, long before the dementia symptoms are present. A higher Erlangen Score was related to an increased risk of conversion from MCI to AD, and progression from SCD to MCI. In our population, almost all of the observed progressive patients without dementia (15 of a total 16 progressive subjects) were characterised by probable and possible AD pathology (the Erlangen Score 2, 3, or 4), but only one patient form this subgroup had no (scored as 0) risk of developing AD. Similar results were presented in the work of Lewczuk *et al*. [13]. This is in accordance with the literature data and reflects the nature of development of Alzheimer's disease.

Our research has shown that an analysis of the concentrations of the CSF biomarkers by using the Erlangen Algorithm Score allows us to determine the likelihood of developing Alzheimer's disease in patients presenting subjective or mild cognitive impairment, even based on a relatively short period of observation. Those patients diagnosed with MCI and SCD who obtained 2-4 points during evaluation with Erlangen Algorithm Score require further observation because of the increased risk of AD development. However, further observation is essential and the probability of conversion to dementia is increased because almost 13% (4 of 31) subjects with SCD progressed to MCI within the relatively short period of more than a year. In the more advanced MCI group, a similar percentage of patients (11.54%, 12 persons) developed AD dementia after 14.33 months, which is similar to the results published by Lewczuk *et al*. (2015) [13]. In our combined group of non-demented progressive only one subject had no underlying Alzheimer's pathology, which confirms that the presence of possible or probable AD in the Erlangen Algorithm Score increases the risk of AD dementia, even in cognitively intact persons. Other data on the Erlangen Score values in the SCD subject progression to more advanced stages is unknown, which makes our results unique.

The Algorithm seems to be also more sensitive in detecting the conversion risk than using only neuroimaging techniques [13,15,24]. The combined hippocampus volumetric measures with AD-CSF biomarker concentrations could increase the specificity and the sensitivity of diagnosis [25], suggesting that $A\beta_{42}$ concentrations and hippocampal volumes may be used in combination to best identify prodromal AD [30]. However, the most recent data suggest that the Aβ level is superior to single biomarker levels or their combination [9].

As we expected, there were some limitations to the study. The subjects were recruited from the memory clinic, which made the results less representative for the whole population. Most of the patients had secondary or university level education. A high level of education of patients with a family history of AD could be an additional factor to report to the memory clinic. The subsequent drawback was the lack of a healthy control group due to ethical reasons, as the procedure of a lumbar puncture is rather invasive. The relatively short period of observation is another disadvantage, but despite this, some results brought interesting conclusions and all subjects from the described group are under our medical control.

Current data suggest that the measuring the $A\beta_{42}/A\beta_{40}$ ratio makes the diagnosis of AD more reliable, but it is very expensive and due to financial reasons, the additional use of the Erlangen Algorithm Score in the interpretation of the raw levels of CSF biomarkers might improve the diagnostic value.

At present, the limitations in applying the CSF biomarkers in daily practice are still related to the difficulties in interpreting the results. It is important to establish methods and protocols to improve early diagnosis of the AD. Determining the biomarkers identifying asymptomatic patients and estimating the risk of AD developing will allow selection of individuals with AD before the stage of dementia

evolves. Patients with a high risk of developing AD are the best group for further clinical research and clinical trials. Furthermore, it is of ethical importance because it is not desirable to include patients with a low risk of developing the disease into research accompanied by the risk of adverse effects. Identification of asymptomatic patients will also be of key importance in the future when causal treatment of Alzheimer's disease will be available

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Disclosure

The authors report no conflict of interest.

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