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Alzheimer's disease with normal CSF biomarkers



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Conclusion

Alzheimer's disease patients with normal CSF biomarkers, defined as in clinical routine, displayed the same cognitive short-term response to ChEI treatment and clinical long-term outcome as patients with pathological CSF biomarkers. These findings must be considered in the definition of future diagnostic criteria for AD.

Background and objectives

Alzheimer's disease (AD) is currently diagnosed clinically using defined symptomatic diagnostic criteria. Pathological levels of CSF biomarkers (i.e. high T-tau and P-tau and low A β 42) have been associated with AD; however, the definition of cut-off values varies. New diagnostic criteria that include the pathological CSF biomarkers have been suggested. Our objective was to determine the proportion of AD patients in a routine clinical population who had normal levels of the CSF biomarkers as defined by clinically set cut-off values.

Methods and subjects

Out-patients (n = 151) with a clinical diagnosis of dementia as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV), and probable or possible AD, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and related Disorders Association (NINCDS-ADRDA, 1984) were included in this study. The number of symptoms according to these criteria and the levels of the CSF biomarkers A β 42, T-tau, and P-tau were evaluated at baseline. Pathological levels of CSF biomarkers were defined as in clinical routine: T-tau > 450 ng/l, P-tau > 60 ng/l and A β 42 < 400 ng/l. In addition, other definitions of previously used cut-off values were described [1, 2].

CSF taps were obtained from the patients and taken at the lumbar L3/L4 or L4/L5 interspace. The CSF samples were frozen at -80°C and stored in polypropylene tubes. The biomarker levels were determined by the xMAP Luminex technology using the INNO-BIA AlzBio3 kit (Innogenetics, Ghent, Belgium).

The patients received cholinesterase inhibitor (ChEI) treatment and were assessed using cognitive tests (MMSE and ADAS-cog) longitudinally for up to 3 years. Short-term ChEI response was measured as cognitive changes after 2 and 6 months. Long-term outcome was expressed as MMSE and ADAS-cog changes per month.

One-way Analysis of Variance (ANOVA) with post hoc Dunnett's t-test was used to compare groups (1, 2 or 3 positive biomarkers) with the normal biomarker group as the reference.

Table 1. Baseline characteristics

Number of patients (n)	151
Gender (males / females)	31% / 69%
Estimated age at onset ^a	72.9 ± 6.8
Age at start of ChEI treatment ^a	75.8 ± 6.3
Duration of AD, years ^a	2.8 ± 2.0
MMSE ^a	21.7 ± 4.5
ADAS-cog ^a	20.6 ± 9.9
CSF A β 42 (ng/l) ^a	389 ± 97
CSF T-Tau (ng/l) ^a	620 ± 349
CSF P-Tau (ng/l) ^a	77 ± 33

^amean ± SD.

References

- Mattsson, N., et al., CSF Biomarkers and Incipient Alzheimer Disease in Patients With Mild Cognitive Impairment. JAMA: The Journal of the American Medical Association, 2009. 302(4): p. 385-393.
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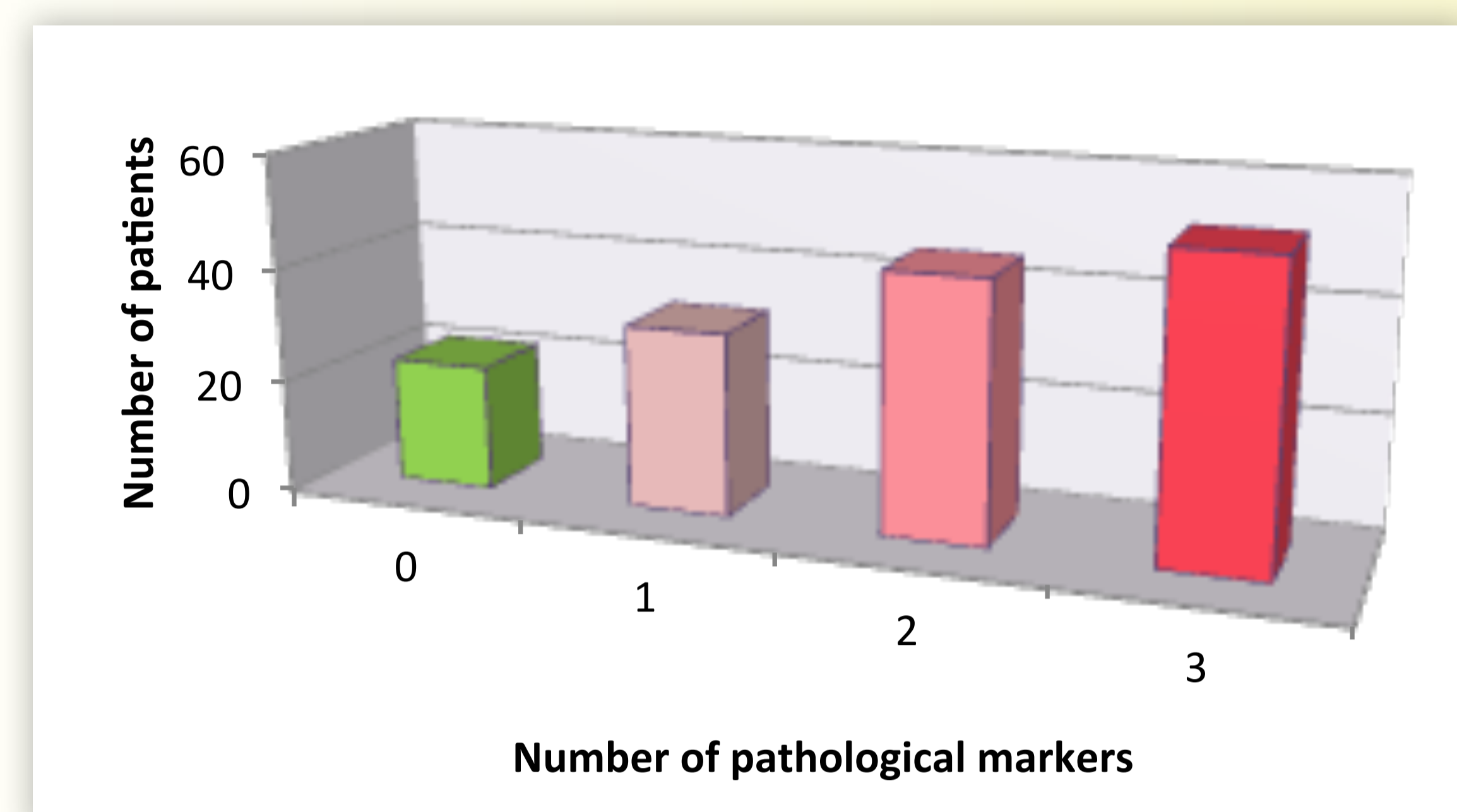
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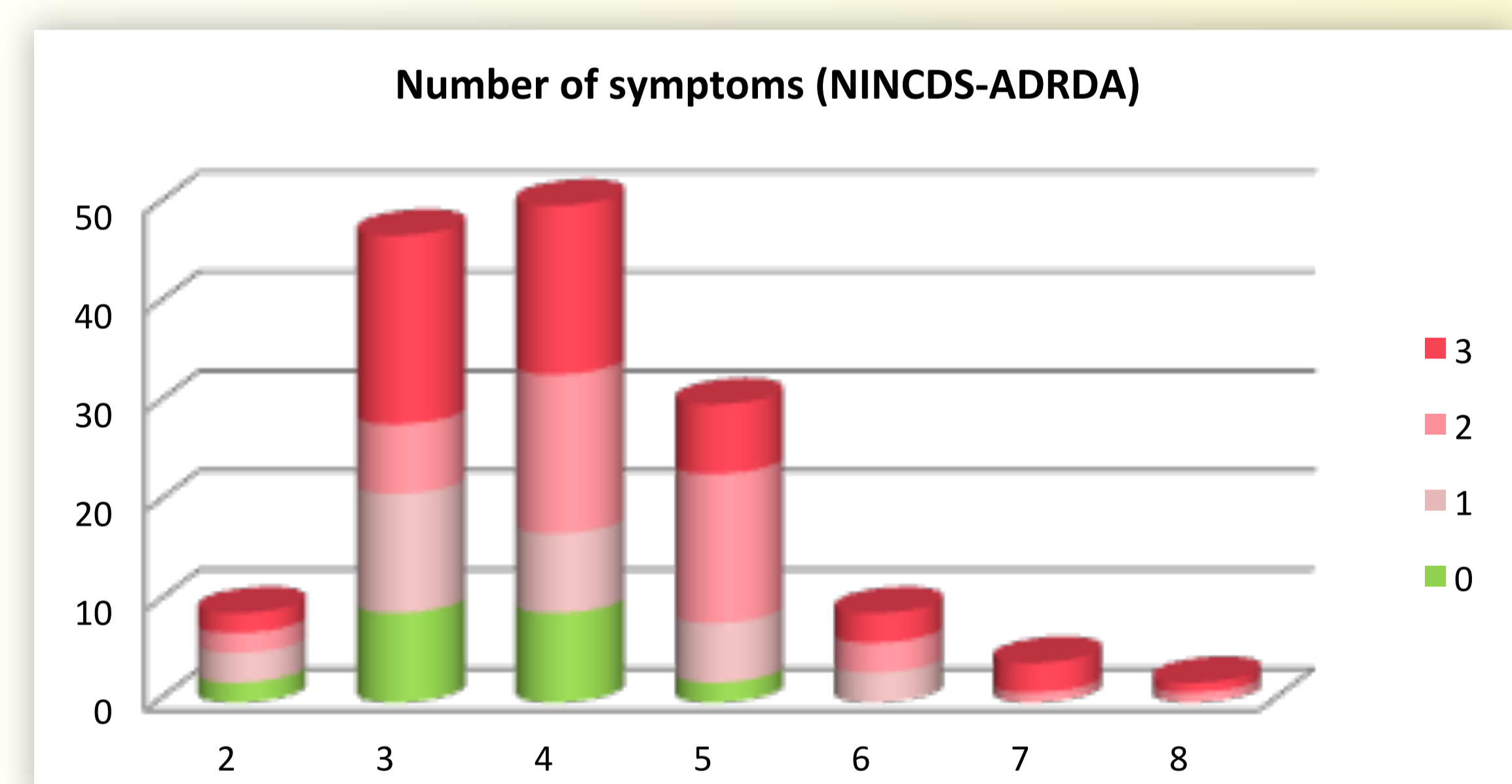
Results

Figure 1. Number of pathological CSF biomarkers



According to the cut-off levels used in this poster, all three CSF biomarkers were normal in 15% of the 151 AD patients. Furthermore, 21% had one, 30% two and 34% three pathological CSF biomarkers.

Figure 2. Number of symptoms according to the clinical criteria of NINCDS-ADRDA.



At baseline, patients with normal CSF biomarkers had fewer symptoms (NINCDS-ADRDA) and a higher MMSE score. However, they displayed the same pre-treatment progression rate, and rate of longitudinal cognitive decline after start of ChEI therapy, as patients with pathological biomarkers.

Furthermore, patients with normal CSF biomarkers did not differ in age of onset, duration of disease, IADL or ADAS-cog at baseline, completion rate or short-term response to treatment compared to those with pathological CSF biomarkers.

Table 2. Percentage of patients with pathological CSF biomarkers using different cut-off values

Number of pathological biomarkers	0	1	2	3
Poster model (T-tau > 450 ng/l, P-tau > 60 ng/l, A β 42 < 400 ng/l)	15%	21%	30%	34%
Hansson ² (T-tau > 350 ng/l, A β 42 < 530 ng/l)	3%	16%	81%	-
Hansson ² (T-tau > 350 ng/l, A β 42 / P-tau < 6.5)	12%	21%	67%	-
Mattsson ¹ (T-tau \geq 320 ng/l, P-tau \geq 52 ng/l, A β 42 \leq 482 ng/l)	4%	11%	10%	75%