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Palmomental reflex a relevant sign in early Alzheimer's disease diagnosis?

Authors

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Abstract

Background: Sophisticated and expensive biomarkers are proposed for the diagnostic of Alzheimer disease (AD). Amyloid process seems to be early in AD and brain amyloid load affects the frontal lobe. Our objective is to determine if certain simple clinical signs especially frontal-related signs could help reach an earlier and better diagnosis.

Methods: In the frame of the 3-City cohort, we conducted a nested case-control study comparing incident cases of Alzheimer's dementia to controls matched for age, sex and education. The standardized neurological exam included extrapyramidal signs (akinesia, rigidity, rest tremor), pyramidal symptoms (spastic rigidity, Babinski reflex), primitive reflexes (snout, palmomentary reflex grasping) and tremor (essential, intentional, head) at the time of diagnosis and two years before.

Results: We compared 106 incident Alzheimer's dementia subjects (mean age at diagnosis 82.2 (SD=5.9); median MMSE at diagnosis=23) to 208 matched controls. In patients younger than 80, palmomentary reflexes were more frequent in Alzheimer's dementia than controls, two years before diagnosis (25.0 vs. 7.0%, $p=0.03$) and at time of diagnosis (30.3 vs. 12.3%, $p=0.02$). No difference was observed for other signs two years before diagnosis or for patients older than 80.

Conclusions: Before diagnosis, the clinical examination of AD patients is not strictly normal, the primitive reflexes appear to be pathological. It might be in connection with the frontal amyloid load at an early stage of the disease. Clinical examination can reveal simple and interesting signs that deserve consideration as the other more invasive and expensive biomarkers.

Background

On the hypothetical dynamic's curve of biomarkers' appearance for the diagnosis of Alzheimer disease (AD)^{1,2}, clinical signs seem to appear late after the positivity of *in vivo* biomarkers reflecting the amyloid process and the Tau neuronal injury. The development of brain imaging amyloid markers, based on the amyloid cascade theory of Hardy^{3,4} gives us anatomical information regarding the amyloid load. The aim is to underline *in vivo* amyloid plaques in the brain regions of interest which reflect the AD process. In the first human study comparing Pittsburgh Compound-B (PIB) retention in 16 mild AD patients versus 9 controls, the PIB retention was increased most prominently in frontal cortex (1.94-fold, $p = 0.0001$) in the AD patients⁵. If large increases were also observed in parietal, temporal and occipital cortices⁵, other studies validated on visual inspection of the PIB images, a greater binding in the orbitofrontal, posterior cingulate and precuneus (for review Saidlitz et al.,⁶). Amyloid load assessed on PET scan may be also a risk marker of progression of healthy and Mild Cognitive Impairment (MCI) subjects to AD⁷⁻⁹. Literature data show that 20 to 30% of healthy elderly subjects have increased amyloid. In these subjects amyloid load progresses during follow-up, as shown in a study¹⁰ which followed 24 non-demented subjects, mean age 79 years, for 1.5 years \pm 6 months and found that PIB retention increased by 0.9% annually. The increase was greater in subjects who had high amyloid deposition at baseline, mainly in the prefrontal, parietal, lateral temporal, occipital, and anterior and posterior cingulate cortices. Moreover, certain regions of amyloid deposits (pre-frontal, posterior cingular, lateral temporal cortices) appear to be more predictive of risk of progression of amnesic MCI subjects toward dementia disorder¹¹. On the other hand, some neuropsychiatric signs like apathy or irritability seem to belong to the spectrum of prodromal AD symptoms^{12, 13}. No study underline the presence of frontal clinical signs at an early stage of AD.

We assume that clinical signs could help in a better and earlier diagnosis of AD and in particular specific clinical signs such as frontal release signs (snout, palmomental, grasping...) in relation with the frontal (pre-frontal, lateral frontal) amyloid load at an early stage¹⁴⁻¹⁶. To address this hypothesis, we explored whether neurological signs could be present at an early stage of AD in a subsample of the French Three-City (3C), a prospective cohort study of non-institutionalized subjects aged 65 and over, followed during 12-years with an exhaustive and systematic clinical examination at each follow-up.

Materials and Methods

Study design

The French 3C study (three French cities: Bordeaux, Montpellier and Dijon) is a population-based study of non-institutionalized subjects aged ≥ 65 aiming to determine the relationship between vascular factors and dementia^{17, 18}. A nested case-control study¹⁹ is designed based on the 2259 participants stemming from the Montpellier cohort followed every two years during 12-years with standardized and detailed neurological examination.

This neurological examination was carried out for all individuals by a trained practitioner at each follow-up. Each practitioner was trained by the same senior neurologist (JT) during all follow-ups. A systematic procedure for the neurological exam was fulfilled by the practitioner. A particular focus on extrapyramidal signs (akinesia, rigidity, rest tremor), pyramidal symptoms (spastic rigidity, Babinski's sign), primitive reflexes (snout, palmomental, grasp) and tremor (essential (action/postural), intentional, head) classified in 0 (absent) or 1 (present) is performed.

To test akinesia, as a change of the initiation and the automatic execution of the movements, the slowing down and the rarity of the harmonious character of the gesture, we analyzed rapid alternative movements, gait impairments and reduced

facial expression (mask-like). For extrapyramidal rigidity, we analyzed the sustained “lead pipe” resistance throughout the range of motion affecting flexor and extensor muscles equally. Cog wheeling may be brought out when the examiner passively moves an elbow or wrist. This sign is increased by reinforcement maneuvers such as having the patient use the opposite hand to trace circles in the air. Asymmetric resting tremor corresponds to regular rhythmic tremor (frequency 4-6 Hertz) observed when the patient sits, hands on the knees. To detect the palmomental reflex, the skin of the patient is scratched near the thenar eminence by a key. When present there is a brief contraction of the ipsilateral mentalis muscle with puckering the chin. The essential tremor included postural- or action-type tremor. It pertains to the abnormal oscillation around the axis when the postural manoeuvre hand in tension is performed. The intentional tremor presents characteristics of cerebellar signs, the tremor appears when patients are asked to touch their nose with their fingers, oscillations are more marked when the target is reached.

The diagnosis of dementia is established at each follow-up using a two-step procedure. First, the evaluation of neuropsychological tests (MMSE, the Isaacs Set Test and the Benton Visual Retention Test) is performed by trained psychologists²⁰ and the subject is systematically examined by a neurologist. Second, an independent committee of neurologists reviewed all potential cases of dementia in order to obtain a consensus based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria and NINCDS-ADRDA criteria for AD diagnosis. We excluded the 41 prevalent dementia cases for which clinical signs before diagnosis were unavailable, and the 66 incident dementia other than AD. Thus, the cases were the incident AD cases that were identified during the 12-year follow-up (n=106). Two controls per case were randomly sampled from the set of those at risk i) under follow-up on the date the case was diagnosed ii) of the same sex, age (± 2.5 years) and educational attainment (4 classes: primary,

secondary, college and university as described in Table 1). We constitute a group of 208 matched controls (4 cases has only 1 matched-controls).”

Statistical analysis

Clinical signs variables are evaluated as binary characteristics. First we compared cases and controls using Chi2 test (for qualitative variables) or Wilcoxon’s test (for quantitative variables). Multiple conditional logistic regressions were used to estimate the odds ratios with their 95 percent confidence intervals in matched cases-control analysis^{21, 22}. We analyzed the neurological signs at time of diagnosis and two years before. Secondary, we performed the same analysis in two groups according to age: < 80 years-old/ ≥80 years old. Analyses were performed using the SAS software (version 9.2, SAS Institute Inc., Cary, NC).

Results

Sample characteristics at time of diagnosis (Table 1 and 2)

In the incident AD cases, the mean age was 82.2 (SD=5.9), 19.8% and were highly educated, the median MMSE was 23 [14-28], 20.4% presented a MMSE ≥26 and 58.3% a MMSE between 21 and 26. All cognitive scores were lower in the AD dementia group than in controls (p<0.001). At baseline, no difference was observed between groups for vascular risk factors (diabetes mellitus, blood pressure, alcohol consumption, tobacco abuse, BMI and presence of cardiovascular diseases) (*data not shown*).

Clinical signs two years before and at the time of the AD dementia diagnosis in the entire population (Table 3)

At time of diagnosis, akinesia (30.7 vs. 17.6%, OR=2.44, p=0.004), palmomental primitive reflex (22.6 vs 12.1%, OR=2.30, p=0.02) and essential tremor (17.3 vs. 8.51%, OR=2.16, p=0.03) were more frequent in incident AD cases than in

controls. Two years before, no clinical sign differed between incident AD cases and controls in the entire population.

Clinical signs in patients younger than 80 years old (Figure 1)

Interestingly, in younger patients (less than 80 years old) the palmomental reflex was more frequent in AD patients than in controls (25.0 vs. 7.0%, $p=0.03$) two years before. This result persists at the time of diagnosis (30.3 vs. 12.3%, $p=0.02$). Akinesia (43.5 vs. 23.8%, $p=0.001$) and essential tremor (21.1 vs. 11.8%, $p=0.035$) were more frequent in older AD patients (≥ 80 years-old) at the time of diagnosis only. No difference was observed for grasp reflexes, Babinski's sign, others types of tremor, plastic or spastic hypertonia, or others neurological clinical signs.

Discussion

To the best of our knowledge, this is the first report highlighting that primitive reflexes were present and relevant for AD diagnosis at an early stage in patients younger than 80 years. Two years before diagnosis, palmomental reflex could help discriminate young AD patients from controls. The palmomental reflex might be an useful warning sign in routine clinical practice. Our results challenge the dogma of the normal clinical examination in AD patients at an early stage of the disease²³.

Primitives reflexes such as palmomental, snout, grasp reflexes are present from birth and can be associated with feeding and attachment to the mother. They disappear as the frontal part of the brain matures. In healthy subjects, the primitive reflexes are often present and the prevalence increases with age as described in the large sample of the Maastricht Aging study²⁴. It seems that primitive reflexes appear commonly after the age of 66 years. As the 3C study included subjects

older than 65, we took into account the effect of age by matching controls to AD cases in regards to age. For specific dementia diagnosis, studies usually report a lack of specificity and sensibility of these reflexes particularly the palmomentals²⁵. However the exact prevalence of such primitive reflexes is unknown because of the variability in the means of eliciting these reflexes and the interpretation of their presence. In dementia patients, the presence of primitive reflexes has been linked to the severity of the dementia in a prospective study of 2914 Canadians over 65, with a higher frequency in patients with severe dementia than at an earlier stage of the disease²⁶. In a systematic description of 204 cases of dementia, primitive reflexes appear to be more indicative of advanced age, severity of the illness and diagnosis of Lewy body disease or mixed dementia²⁷. In the present study, we unveiled interestingly that palmomentals primitive reflexes were pathologic early on in the AD process in younger patients younger than 80 years, a point that had never been examined in previous studies. The reasons why these clinical signs were only pathologic in younger patients remain hypothetical but one explanation might be the high prevalence of amyloid lesions in the frontal area in normal elderly people, observed for example in amyloid imaging studies, contributing to decreasing the difference between AD and non-AD in older people. Another hypothetical explanation might reside in the fact that older patients present a different AD clinical phenotype with less frontal-related signs and more akinetic symptoms related to the impact of vascular mixed brain lesions. The palmomentals reflexes could be interpreted as a frontal-released reflex. Some neuropsychological and brain imaging studies underlined that frontal areas are pathologic at a prodromal stage of the disease. Frontal-related apathy could be considered as an early biomarker of AD diagnosis²⁸⁻³⁰. In the same way, the amyloid PET-scan studies at a prodromal stage of AD, revealed that amyloid load is predominant on frontal areas such as dorsolateral frontal areas⁷. In this study, the diagnosis of Alzheimer's dementia is based on the NINCDS-ADRDA diagnosis criteria and on

a consensus adjudicative committee. As all the converters and/or controls has not undergone brain imaging to exclude vascular changes in frontal lobes, we could not exclude that some vascular lesions are the cause of the positivity of frontal release signs.

A major strength of our work is the framework of a longitudinal follow-up and systematic neurological exam implemented in the 3C-Montpellier cohort. Clinical signs were documented at each wave and can be studied two years before the diagnosis. So interpretation is not influenced by cognitive complaint or status and reflect the AD prodromal phase. However, we cannot exclude inter-operator differences in the interpretation of the presence of each clinical sign despite the fact that all physicians who examined participants have been trained to standardized the exam in the Neurology unit (JT, AG) associated closely to the epidemiological team.

Conclusion

Primitive reflexes can be tested easily and rapidly in clinical routine. Even if the sensibility of these signs is far from perfect, their presence may alert the clinician to the possibility of brain pathology, even at an early stage. The standardized examination with primitive reflexes evaluation should be included or re-included in the neurological bedside screening of patients with early AD degenerative process.

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Details of contributors: Individual contributions to the manuscript

A. Gabelle: study concept; analysis and interpretation of the data; drafting /revising the manuscript.

L.A Gutierrez: acquisition of data; analysis and interpretation of the data; statistical analysis; drafting/revising the manuscript.

JF Dartigues: study supervision; management of dementia diagnosis consensus, drafting/revising the manuscript;

K Ritchie: study supervision; drafting/revising the manuscript.

J. Touchon: study supervision; training neurologists, drafting/revising the manuscript.

C. Berr: data acquisition; analysis and interpretation of the data; statistical analysis; study concept; study supervision; drafting/revising the manuscript.

Name of the guarantor: C Berr

All patients gave their written informed **consent** to participate in this research study.

The study protocol was approved by the **Ethical Committee** of the Institutional Review Board at Kremlin-Bicêtre University Medical Center.

Table 1: Characteristics of AD cases and matched controls presented on the whole population

	Whole sample					<80 years				
	Matched controls		AD cases		p	Matched controls		AD cases		p
	n	Mean (Std)	n	Mean (Std)		n	Mean (Std)	n	Mean (Std)	
Age at diagnosis	208	81.53 (5.63)	106	82.16 (5.91)	0.44	74	75.39 (3.0)	33	75.36 (3.24)	0.96
Sex (men)	69	33.17	35	33.02	0.98	27	36.49	13	39.39	0.77
Years of education										
Primary	70	33.65	36	33.96	1	35	47.3	16	48.48	1
Secondary	50	24.04	25	23.58		10	13.51	5	15.15	
College	47	22.6	24	22.64		15	20.27	6	18.18	
University	41	19.71	21	19.81		14	18.92	6	18.18	

and in the two age-groups: Comparisons between

AD cases and matched controls.

Table 2: Neuropsychological scores (Median [Min-Max]) in the whole population and in the two age-groups: Comparisons between AD cases and matched controls.

	Whole sample			<80 years			≥80 years		
	Matched controls	AD cases	p	Matched controls	AD cases	p	Matched controls	AD cases	p
	N=208	N=106		N=74	N=33		N=134	N=73	
<u>At time of diagnosis</u>									
					23.0				
MMSE *	28.0 [22.0-30.0]	23.0 [14.0-28.0]	<0.001	27.5 [23.0-30.0]	[14.0-28.0]	<0.001	28.0 [22.0-30.0]	23.0 [15.0-28.0]	<0.001
BVRT**	12.0 [4.0-15.0]	10.0 [5.0-14.0]	<0.001	12.0 [7.0-15.0]	10.0 [5.0-13.0]	<0.001	11.0 [4.0-15.0]	10.0 [5.0-14.0]	<0.001
				34.00	26.0				
IST***	32.0 [8.0-49.0]	24.5 [10.0-40.0]	<0.001	[21.0-49.0]	[12.0-44.0]	<0.001	32.0 [8.0-48.0]	24.0 [10.0-42.0]	<0.001
<u>2 years before time of diagnosis</u>									
	N=193	N=93		N=74	N=31		N=122	N=61	
					26.0			26.00	
MMSE*	28.0 [20.0-30.0]	26.0 [20.0-30.0]	<0.001	28.0 [22.0-30.0]	[20.0-30.0]	0.01	28.0 [20.0-30.0]	[21.0-30.0]	<0.001
BVRT**	12.0 [7.0-15.0]	11.0 [4.0-15.0]	<0.001	12.0 [8.00-15.0]	11.0 [5.0-15.0]	0.02	12.0 [7.0-15.0]	11.00 [4.0-15.0]	0.001
					27.5				
IST***	32.0 [19.0-54.0]	27.0 [9.0-44.0]	<0.001	20.0 [33.0-46.0]	[13.0-44.0]	<0.001	32.0 [19.0-54.0]	27.00 [9.0-41.0]	<0.001

* MMSE :Mini Mental State Examination

** BVRT : Benton Visual Retention Test

*** IST: Isaac Set Test score at 15 seconds

Table 3: Frequency of neurological clinical signs between incident AD cases and matched controls at time of diagnosis and two years before (p value are based on results of conditional logistic regression comparing AD and controls).

	At time of diagnosis				Two years before	
	Matched controls N=208	AD cases N=106	OR [CI 95%]	p	Matched controls N=208	AD cases N=106
Akinesia	35 (17.6%)	31 (30.7%)	2.44 [1.32-4.49]	0.004	30 (15.6%)	19(21.1%)
Snout reflex	55 (27.6%)	37(36.3%)	1.72 [0.91-3.27]	0.01	56 (29.3%)	35 (38.9%)
Palmomentary reflex	24 (12.1%)	23 (22.6%)	2.30 [1.17-4.52]	0.02	22 (11.5%)	17 (18.9%)
Rigidity	12 (6.03%)	12 (11.8%)	2.14 [0.92-5.01]	0.08	10 (5.21%)	6 (6.67%)
Essential tremor	17 (8.50%)	18 (17.3%)	2.16 [1.06-4.41]	0.03	13 (6.77%)	9 (10.0%)

Figure 1: Effects of primitive reflexes (palmomental, snout) and akinesia clinical signs between 106 incident AD cases and 208 matched controls in two age groups (< or ≥ 80 years old) two years before or at time of AD diagnosis.

