Relationships Between Psychological Measurements and Cerebral Organic Changes in Alzheimer's Disease

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SUMMARY: *Twenty-two patients were carefully defined as having progressive dementia without other known cause and not complicated by clinical or laboratory evidence of multiinfarct dementia. Their degree of dementia measured by the ESD correlated highly with EEG disturbance (r= -0.79). The LPRS correlated 0.73 with ventricular enlargement. Although the EEG and CT scan only correlated significantly with each other in advanced cases, a combined index of EEG and CT Scan change, (Physical Meaasures Index) achieved a correlation of 0.93 with a combined index of psychological change (Psychological Measures Index). The results indicate the possibility of using physical and psychological measures to monitor quantitative change in Alzheimer's Disease, the EEG contributing more initially and the CT scan more in the most advanced cases.*

RÉSUMÉ: *Nous avons défini avec soins les charactéristiques de 22 patients présentant avec une démence progressive sans cause apparente et non compliqués par des évidences cliniques ou de laboratoire de démence consécutive à de multiples ramolissements. Le degré de démence fut mesuré par le ESD et était en corrélation importante avec le degré de trouble à l'EEG (r=-0.79). Le LPRS montrait une corrélation de 0.73 avec l'agrandissement des ventricules. Même si l'EEG et la tomodensitomètrie n'étaient reliés de façon significative que chez les cas avancés, nous avons montré qu'un index combiné d'EEG et de tomodensitomètrie (Index des mesures physiques) atteint un coefficient de corrélation de 0.93 avec l'index combiné des changements psychologiques (Index des mesures psychologiques). Les résultats indiquent la possibilité d'employer des mesures physiques et psychologiques pour suivre les changements quantitatifs dans la maladie d'Alzheimer. Au début l'EEG contribue plus à cette évaluation, alors que la tomodensitomètrie est plus utile pour les cas avancés.*

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In dementing illnesses the principal disability is intellectual decline. It is important to know whether the degree of disability is paralleled by corresponding quantitative brain changes. If so, the physical process will advance and the mental state will decline in parallel. If a discrepancy exists it may be due to environmental or emotional influences on the patient's well-being; or it may be due to the presence of a second physical disturbance which exacerbates or modifies the dementia. In either case it can be useful for further investigation and management to know if the psychological indices of change are in accordance with the physical changes. As treatments are suggested for dementias e.g., acetylcholine precursors for Alzheimer's disease, it may be useful to have effective techniques available for assessing the extent of the disease process and comparing it with the psychological state before, during, and after treatment.

At the London Psychiatric Hospital, two measures have been developed for the cognitive functions and behavioral state of patients with moderately severe and severe dementia.

One, the Extended Scale for Dementia (E.S.D.) was developed for this study from the scale of Mattis (Coblentz et al., 1973) after an examination of other available tests. It uses previously validated items with some modifications for testing cognitive function of the elderly. It has a Pearson correlation coefficient of 0.94 for six week test-retest reliability (Hersch, 1979). It classifies patients with a clinical diagnosis of dementia from others with a diganosis of functional psychiatric illness with 86% accuracy.

The second scale, the London

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Psychogeriatric Rating Scale (L.P.R.S.), is a 36-item one which has inter-rater reliability of Pearson's r = 0.92 (four subscales of the test range in reliability from .80 to .94). It distinguishes specifically ($p < .001$) between patient groups in respect to ward placement, the independent diagnosis of the presence of dementia versus a functional psychosis, and outcome on discharge (Hersch et al., 1978). High scores on the E.S.D. with low scores on the L.P.R.S. indicate better performance. The two tests correlate -0.93 with each other (Hersch, 1979) and the concurrent validity of both may further be judged from the correlations with physical indices to be described below. The Extended Scale for Dementia requires responses from the patient for its items and very severely demented cases have to be classified as 'untestable' on it, but the LPRS is capable of application to patients with all grades of dementia.

Two particular indices of physical change, namely the EEG and the CT Scan are of interest. The EEG was probably first noted by McAdam and Robinson (1957) to be related to the degree of dementia. In an early study, combining patients with Alzheimer's Disease and atherosclerotic disease, they demonstrated a correlation of 0.79 between EEG change and clinical rating ($p < 0.01$). Both clinical and EEG ratings were found to be sensitive indicators of prognosis. Letemendia and Pampiglione (1958) reported 17 patients with histological verification. They observed absent or scanty alpha rhythms and generalized 2-7 c/s activity among other changes, and noted that the EEG changes were fairly uniform and might help with differential diagnosis. Gordon and Sim (1967) who studied 56 demented patients (of whom 35 had biopsy evidence of Alzheimer's Disease) found no confirmed Alzheimer's Disease patient with a normal EEG; but only 6 out of 20 patients with presenile dementia negative for Alzheimer's Disease had an abnormal EEG. They also showed a progression of EEG change with Alzheimer's Disease and some relationship between the degree of EEG change and the degree of dementia. They further found more EEG disturbance in cases of longer duration and in cases with greater degrees of atrophy. Muller and Kral (1967) demonstrated the particular association of both early and late Alzheimer's Disease with bilateral synchronous slow-wave complexes. These occurred in 33% of advanced Alzheimer's Disease patients and 16% of patients with multiinfarct disease. Kazniak et al. (1978) showed that in patients with progressive dementia and no major focal signs the EEG was not always abnormal but that the degree of abnormality strongly indicated mortality at one year. Twelve out of 16 with severe diffuse slowing or left temporal slowing were dead compared with 2 out of 15 with normal EEGs or mild diffuse slowing after that time. On the basis of a discriminant function test derived from psychometric measures these authors correctly classified 97% of 35 patients at the end of one year from testing.

Roberts et al. (1978) demonstrated a relationship between severity of abnormality in the EEG and mental impairment in non-vascular dementia, as well as one between localized EEG change and mental impairment in vascular dementia. Degrees of dementia were also related to cortical atrophy in non-vascular dementia. Biopsy or post-mortem data are not reported in the latter three studies. Overall there is evidence that progressive dementia of the Alzheimer type is associated with progressive EEG changes and the work of several groups indicates a relationship between diffuse EEG changes and mortality in patients with presumed Alzheimer's Disease.

Some radiological features are also changed in dementia patients. Atrophy of gyri has not been shown to be strongly correlated with dementia since it can occur in the presence of normal intellectual functioning, and the reverse — dementia without atrophy — may also be found. Nielsen et al. (1966) have shown some relationship between cortical atrophy on pneumoencephalography and intellectual impairment. However, Mann (1973) demonstrated that although in general decisions about dementia based upon apparent atrophy were not reliable, enlargement of the diameter of the third ventricle correlated significantly with the correct diagnosis of dementia. Significant relationships are described between ventricular enlargement and psychometric test performance by other authors (Matthews and Booker, 1972; McFie, 1960; and Willanger, 1970).

CT Scans have made this field of inquiry easier and more attractive, but their availability and harmlessness have emphasized an obvious problem viz: how to quantify irregular two dimensional shapes which are presumed to reflect three dimensional cortical atrophy. However, correlations have been shown between CT scan atrophy and dementia diagnosed clinically (Fox et al., 1975) or psychometric cognitive changes (Kazniak et al., 1975). In a study by Roberts and Caird (1976) the degree of ventricular enlargement was found to be correlated with mental impairment in non-vascular dementia and Roberts et al. (1978) showed with non-vascular dementia that mild and moderate dementias were associated with smaller ventricular sizes than severe dementias. Visible infarcts were clearly associated with the largest increase in ventricular size.

We report here the first results of a correlational study in Alzheimer's Disease, taking into account psychometric measures, EEG semiquantitative assessment, and CT scan measurements.

PATIENTS AND METHODS

A sample of 7 males and 13 females from the inpatient psychogeriatric unit of London Psychiatric Hospital and 2 male out-patients was studied. They all satisfied the following criteria.

All had progressive dementia without known cause. Episodic changes, raised blood pressure, or neurological signs of stroke excluded patients from the sample as did signs of infarct on the CT scans. Eighteen patients had a CT scan.

Seventeen patients (not all the same as those who had the CT scan) had EEGs, 20 patients had the ESD administered or attempted and 20 patients had LPRS scores.

The EEGs were interpreted (WTB) without knowledge of the patients' history or condition, and without knowing that the patient was de-

mented. Any excessive delta and theta activity for age was recognized in a classification system as "Delta" and "Dysrhythmia" respectively and graded I, II, and III according to the quantity of the activity beyond what was normally accepted for age. The distribution of the abnormal activity — focal, regional or diffuse — was also included. A separate classification, Dysrhythmia Grade IV, was given for the presence of epileptiform potentials including spikes. The sum of EEG dysrhythmia and delta activity was arbitrarily utilized as a measure of total EEG disturbance. Although Grade IV in the dysrhythmia classification covered the occurrence of spikes, the latter were also noted separately. The system was based on that of Klass (1971).

CT abnormality was graded for ventricular enlargement by adding together the bifrontal index and the bicaudate index for each patient. To obtain these indices, the lowest slice clearly showing the frontal horns was taken and the widest distance measured between the lateral walls of the frontal horns (bf) and the narrowest distance between the caudate heads (bc). The lines of each of these measurements were extended to the inner table of the skull and the width of the brain in each situation was measured (B and B^1, respectively). The combined bifrontal-bicaudate index is given by $\frac{bf}{B} + \frac{bc}{B^1}$

This is a combination of the two indices utilized by Sarwar et al. (1978).

TABLE 1

Mean Scores for Psychometric and Physical Measures

	N	Total	Confusion/Mental Subscale	
L.P.R.S.*	18	55.89 ± 18.18	61.11 ± 18.10	
E.S.D.**	18	94.55 ± 63.17		
		Dysrhythmia	Delta	Total
E.E.G.	17	2.53 ± 1.7	.76 ± .75	3.29 ± 2.32
		$\frac{bf}{B} + \frac{bc}{B^1}$	Convexity Sulci	Sylvian Sulci
CT Scan	18	0.56 ± 0.08	2.5 ± .62	3.0 ± .59

* L.P.R.S. = London Psychogeriatric Rating Scale
** E.S.D. = Extended Scale for Dementia

TABLE 2

Significant Correlations (r) Obtained for 'Pure' Alzheimer Group with Corresponding Sample Sizes (N)

	ESD		LPRS				ILLNESS DURATION		EEG		MBI	
			Total Score		Changes in Total Score				Presence of Spikes		(Mental Behavioral Index) — from ESD and LPRS	
EEG	r	(N)	r	(N)	r	(N)	r	(N)	r	(N)	r	(N)
Δ grade	-.62**	(15)	.49	(14)	.64**	(10)	.32	(17)				
Dysrhythmia grade	-.79**		.49		.64*		.49*					
Total	-.77**		.51*		.67*		.47*					
Presence of Spikes	-.69**		.45		.45		.60**					
CT												
Ventricle Measure $\frac{bf}{B} + \frac{bc}{B^1}$	-.58*	(16)	.73**	(16)	NS	(10)	.40	(18)	.30	(15)		
Sulci Atrophy at Sylvian Fissure	NS		.59*		NS		NS		NS			
Convexity of Sulci at Surface	-.44		NS		NS		.61**		.56*			
ESD			-.82**	(16)	-.43	(13)	-.61**	(18)				
PMI (Physical Measures Index) — from EEG and CT											.93**	(9)

* — $p < .05$
** — $p < .01$

The widest diameter of sulci at the convexity and at the Sylvian fissure was also recorded.

RESULTS

Table 1 shows the mean values and standard deviations obtained. Table 2 shows the significant correlations obtained. The LPRS and ESD correlate well inversely with each other ($r = -.82$, $p < 0.01$). They both correlate with the EEG: E.S.D. with total EEG change, $r = -.58$, $p < 0.01$; L.P.R.S., $r = .51$, $p < .05$. The ESD, which is perhaps a better measure in the less severe cases than the LPRS, correlates more with the EEG than does the other test. The LPRS and ESD both correlate well with the ventricular diameter as measured by the bifrontal bicaudate index but the LPRS correlates better (LPRS $r = .73$, $p < .01$; ESD $r = -.58$, $p < .05$). These results are appropriate in that the LPRS is able to measure more advanced change than the ESD. Thus, the EEG which is a sign of abnormal activity correlates more with the early dementing changes; the LPRS as a measure of later dementing changes correlates more with the evidence of loss of parenchyma.

A combined physical measures index was derived as follows: Z-scores* for the EEG and CT Scan ratings were summed for each case. Z-scores for the LPRS were likewise summed with those for the ESD (correcting for the negative ESD sign) to derive a combined mental-behavioral index. The combined Z-scores on the physical measures for each case were then correlated with those for the psychological measures, achieving, as shown, a very high degree of concordance between the two combined indices ($r = 0.93$, $p < 0.01$). The numbers are small because not all patients could take the ESD.

There are a number of other findings of interest. In the few patients who have so far been re-tested the degree of abnormality of EEG is proportional to the rate of psychological change. This is shown in the table as the correlation between LPRS and EEG disturbances and is significant at the level $p < .05$. The duration of illness correlates with EEG spikes and more weakly with theta EEG abnormality (dysrhythmia grades). Duration further correlates with CT scan results, the strongest correlation being with atrophy of sulci at the convexity. ($P < 0.01$). Lastly, spikes in the EEG correlate with cortical cerebral changes in the CT scan, namely, convexity atrophy. ($P < .05$). Apart from this, the CT scan measurements, especially the bf-bc index, do not correlate with the EEG.

DISCUSSION

Fox et al., (1979) have concluded that the correlation between the amount of cognitive dysfunction and cerebral atrophy is positive in dementia, but relatively weak. (Kazniak et al., 1979). Our own findings agree that a relationship exists and indicate that it is strongest with the more advanced degree of dementia. At that point, the relationship is substantial. This phenomenon is probably manifest because the LPRS which correlates so highly with increase in ventricular diameter is a rating scale capable of quantifying changes in the more advanced cases.

From the point of view of early diagnosis the EEG is evidently more sensitive than the CT scan. Even so there is a need for a means of identification of Alzheimer's Disease before the process is so advanced as to produce change in the routine EEG and signs of deterioration as measured by the ESD. At the earliest stages of Alzheimer's Disease where the minimal changes in personality or intellectual ability, as shown for example by the WAIS, are present no test or physical measure is available to confirm the diagnosis. The dementia is probably highly correlated with changes in cerebral acetyl-choline metabolism (Perry et al., 1978). If treatment becomes available for Alzheimer's Disease, cerebral biopsy for biochemical examination as well as neuropathology may have to be considered as a technique for supporting the diagnosis. This would become necessary if the treatment carried some risks which patients without Alzheimer's Disease ought to avoid. Once the diagnosis of early Alzheimer's Disease is established, quantitative change can be monitored using the indices which we have employed.

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*Z-scores are scores transformed to a mean of zero and a standard deviation of one. Their purpose is to equalize the units of measurement for different tests.

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