

AN ALGORITHMIC APPROACH TO THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA

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Abstract

The careful definition of cases is fundamental to diagnosis and to any study of cognitive, behavioural and functional problems in dementia. This paper presents an algorithmic approach which mimics a crucial component of diagnostic decision-making: symptoms and signs do not occur independently, but are conditioned on each other. First, we examine whether the conditioned items can be assembled to yield a differential diagnosis of dementia which corresponds to clinical diagnoses, and second, we explore whether subjects whose algorithmic profiles do not fit the clinical diagnoses form new discernable patterns. Such a technique offers two advantages: it allows for the development of validation protocols which are crucial to epidemiological studies, and it allows for the analysis of new patterns of signs and symptoms for emerging criteria of dementia subtypes. This approach has the potential to refine and enhance criteria for the differential diagnosis of dementia and to have an impact on case identification and assessment, particularly in large epidemiologic studies.

One of the more daunting challenges in assembling large epidemiologic databases for dementia studies is that of the validity of the diagnoses. Given the absence of definitive antemortem biological markers, validity is often assured by testing the inter-rater reliability of expert judgement about particular cases [1-8]. While sound, this method has certain limitations arising from the practical difficulties of subjecting individuals to two independent expert evaluations. In consequence, it is possible to carry out such testing on only a limited number of subjects.

An alternative method to assessing the validity of diagnoses is to examine how closely cases conform to a diagnostic algorithm. This approach, used in the Canadian Study of Health and Aging (CSHA), allowed each of the 2914 people to be evaluated [7]. The initial CSHA algorithm was based on two principles. The first was that the criteria for the dementia syndrome and its aetiologic types could be operationalized from the dataset, so that the algorithm could check that the final diagnoses conformed with the listed criteria (e.g. that memory impairment was coded as being present in dementia cases). The second was the internal consistency of the items in the database (e.g. if hypertension was reported as present for the Hachinski score, it should also have been coded as present in the clinical history or on examination). As reported elsewhere, this algorithmic approach resulted in a very consistent recording of dementia symptoms and high expert inter-rater reliability [8,9].

More recently, however, we have begun to explore an alternative approach to dementia algorithms. This new approach is rooted in an increasing appreciation of the heterogeneity of dementia and its sub-types, as reflected both in revisions to the criteria for the diagnosis of dementia syndrome [10,11] and in the modification and development of new criteria for the aetiologic diagnosis of dementia [12-31]. With this appreciation came the pragmatic question of whether new criteria rendered existing datasets obsolete (a question of far-reaching scientific and financial implications) or whether existing databases could be in some way “reworked” to allow insights from the new criteria to be realised. Clearly such a question cannot in the first instance be addressed by re-evaluating patients, but requires methods of looking at relationships between existing database items.

One approach to examining relationships in existing databases is through a technique such as principal component analysis, or partial least squares as described by Gottfries et al [17]. Such an approach allows for the identification of the presence of relationships between variables, but does not differentiate between the types of relationships. Additionally, as with attempts at expert-based decision models [32-35], including our own diagnostic checking algorithm [7,8], such an approach does not recognize what is foundational to clinical reasoning: symptoms and signs do not occur independently, but are conditional on each other. Consider, for example, the case of interpreting focal signs. Current decision-making models rely on a dichotomized “Focal signs: Yes/No” decision which is devoid of a clinical context. Thus a lone increased muscle stretch reflex may have no significance, or much significance, depending on its relationship to abnormalities in the neurologic, medical or cognitive examination, or to items from the history. We suggest that, by examining the conditioning effects of patterns of symptoms and signs, it should be possible to mimic usual diagnostic interpretation. Such an approach offers two advantages: it allows for the development of validation protocols (crucial to such large epidemiologic studies) and, it allows for the analysis of new patterns of symptoms and signs.

More recently, as reported in detail elsewhere [36] we examined constellations of symptoms and signs in different types of dementia. Briefly, we developed a means whereby symptoms and signs (which we shall refer to generically as “items”) can be shown to be conditioned on each other. As expected, the pattern of conditioning (the “coordination” of the items) varied by diagnosis. For example, borrowing our terms from epidemiology, as a given item is present, the probability that another item is present systematically increases (“synergism”) or decreases (“antagonism”). Of note, particular diagnoses give rise to discernible patterns of synergy and antagonism. For example, the coordination of items in severe Alzheimer’s disease was found to be distinct from the coordination of items in severe vascular dementia. Additionally, we found that there was sufficient redundancy in the database that the patterns of coordination could be discerned with comparatively few items.

In the current report, we extend this work in two ways. First, we examine heuristically whether the (conditioned) items can be assembled to yield a differential diagnosis of dementia which corresponds to the clinical diagnoses, and second, and perhaps of greater interest, we explore whether subjects whose algorithmic profiles do not fit the clinical diagnoses form new discernable patterns.

Methods

Population Database

The Canadian Study of Health and Aging (CSHA) database offers a large representative sample of people aged 65 and over diagnosed by standard method [7]. The CSHA clinical assessment collected 789 items of information on each individual, including a cognitive function and mental status exam (the Modified Mini Mental State Examination, 3MS) [37], a nurses's exam and CAMDEX informant interview [38], an extensive medical history and physical exam performed by study physicians [8]. The clinical assessment included a neurological exam which explored signs relevant to degenerative and vascular dementias, and a physical exam of signs relevant to systemic conditions that could cause chronic encephalopathy. The neurological component paid particular attention to nine separate release signs, ten cranial nerve signs, fourteen motor system signs, seven sensory system signs, and twelve muscle stretch reflexes. The physical exam included evaluation of the patient's state of consciousness, general appearance, as well as the peripheral pulses, and signs of cardiovascular, and thyroid problems. The medical history included a comprehensive list of items, many of which were obtained from two sources: the physician's examination and medical history of the subject, as well as a CAMDEX informant interview conducted by the study nurse. These items include a record of changes in personality, memory, mood, everyday activities and continence, as well as the onset and course of the cognitive impairment or dementia. Depression was assessed, as well as the presence of hallucinations or delusions, nocturnal confusion, emotional, verbal or physical agitation, myoclonus, presence of seizures, syncope, falls, resting and active tremors, dyskinesias and akinesia. In addition, a history of several problems including stroke, thyroid disease, diabetes, intermittent claudication, focal neurological symptoms, arterial hypertension, cardiac symptoms, head trauma, headaches, alcohol or substance abuse, unexplained weight change, gastro-intestinal and urinary complaints, malignancy, and vision or hearing loss, was recorded.

The CSHA identified three main diagnostic categories: cognitively normal, cognitively impaired but not dementia (CIND), and dementia. ICD-10 was used to evaluate severity. We restricted our analysis for this paper to the 1132 cases diagnosed with dementia. To arrive at more specific distinctive characterizations of these diagnostic categories, probable Alzheimer's disease (AD) and vascular dementia (VaD) were analysed by severity. Four types of possible Alzheimer's disease (with atypical presentation, with vascular component, with parkinsonism, with coexisting illness possibly contributing to dementia) were treated as distinct entities to investigate their unique characteristics.

The importance of the symptoms and signs for each specific diagnosis and group membership are analysed by comparing how significantly these variables distinguish among specific diagnostic sub-groups. Redundancies in the variables were identified which allowed us to arrive at a reduced set of more efficient and effective clinical items [36]. The initial version of the diagnostic algorithm is based on significant characteristics which identify rules of diagnosis.

Analysis

Let $p_i(X_j)$ be the probability that a patient from the i -th diagnostic group has the symptom X_j , where $i = 1, \dots, N$, N is the number of diagnostic groups, and $j = 1, \dots, M$, where M is the number of binary symptoms and signs. The diagnostic algorithm is represented by a set (configuration) of symptoms and signs sufficient for each diagnosis. This set includes a subset of signs which are present ($X_j = 1$) or absent ($X_j = 0$). The probability of the presence of symptom X_j ($X_j = 1$) is $p(X_j)$, while the probability of the absence of the symptoms ($X_j = 0$) is $1 - p(X_j)$. We let $q(X_j)$ denote the probability of the presence $p(X_j)$ or absence $1 - p(X_j)$ of the sign X_j . Let

$$q_i(X_j) = \begin{cases} p_i(X_j), & X_j = 1 \\ 1 - p_i(X_j), & X_j = 0 \end{cases} \quad (1)$$

Let $\{X\}$ represent the set of symptoms and signs. Let $J \subset \{X\}$ denote the subset of symptoms and signs which are sufficient to determine the diagnosis. For example, $J = \{X_2, X_3, \bar{X}_9, X_{21}\}$ means that $X_2 = 1, X_3 = 1, X_9 = 0, X_{21} = 1$. In order to estimate a product which incorporates the probability of a combination of signs and symptoms, we introduce r_i as the infimum (lowest boundary) of the probability of the combination of symptoms and signs, where

$$r_i = \prod_{j \in J} q_i(X_j). \quad (2)$$

The value of this product may be interpreted as a probability that a patient from the i -th diagnostic group has a combination of symptoms J , assuming statistical independence between the signs. In the case of dependence, the probability of the combination of signs will be greater than r_i . Thus, if the algorithm works well under this assumption, it will also work at least as well and perhaps better if there is dependence. Briefly, the assumption of independence provides us with the most conservative estimate of the lowest boundaries (i.e., the worse case scenario). In the case of independence, r_i is equal to the exact probability of the combination of signs.

Letting z_i be the order statistic for r_i , for example, $z_1 = \min_i(r_i), z_N = \max_i(r_i)$, we looked for the combination of signs and symptoms which provided the maximum probability for the diagnosis. Moreover, we suggest that the value of the probability of the diagnosis (which is the maximum probability z_N) must differ significantly from the rest of the probabilities $z_i, i=1, \dots, N-1$. The null hypothesis is determined by the condition that z_N belongs to the same population as the rest z_i . The nonparametric criteria, τ , was calculated as the difference between the maximum value and the next (after the maximum) value, divided by the difference between maximum and minimum (range) [39],

$$\tau = \frac{z_N - z_{N-1}}{z_N - z_1}. \quad (3)$$

This ratio lies between 0 and 1. A value close to 1 indicates that the maximum probability differs sharply from the others, and this diagnosis is then selected. A ratio close to 0 indicates that the maximum value does not differ significantly from the next closest maximum value, i.e., the probabilities for the two diagnoses do not differ, therefore the considered combination of symptoms and signs does not significantly distinguish between the diagnoses. We then look for a more appropriate combination of items. If the value of this criterion exceeds the critical value, $\tau > \tau_{crit}$ (at the 0.05 level for $N=11$, $\tau_{crit}=0.392$, at the 0.01 level, $\tau_{crit}=0.502$ [39]), the null hypothesis is rejected (N represents the number of diagnostic categories). Thus, an alternative hypothesis (z_N is significantly different from the rest z_i) is accepted and the combination of symptoms and signs, J , is considered as a diagnostic configuration.

An example of this method

Table 1 presents the probability matrix with the symptoms and signs in the rows and the diagnostic categories in the columns. We want to check all possible combinations of symptoms and signs which distinguish for each diagnosis. For example, if we consider the diagnostic category Parkinson's dementia (PD), we can see that the maximum probability = .920 for the item 'impaired abstract thinking'. However, it is evident that the probability for this symptom remains consistently high across the diagnostic categories. We reject this item as it appears to offer little diagnostic discrimination. We then select a combination of three items with maximum probabilities, facial bradykinesia ($p = .846$), increased limb tone ($p = .846$) and limb bradykinesia ($p = .826$).

We calculate the product $r_i = p(\text{facial bradykinesia}) * p(\text{limb bradykinesia}) * p(\text{increased limb tone})$ for each $i = 1, \dots, 11$. The values for r_i , which respectively match the order of diagnoses along Table 1 (i.e., the first is Mild AD, the second is Moderate AD, ..., PD is the eleventh diagnosis): are: .0001, .0002, .0254, .000, .0027, .4715, .0012, .0035, .0064, .1293, .5912. We then calculate $\tau = (.5912 - .4715) / (.5912 - .0001) = .2025$, which is not sufficient to meet the critical value.

Therefore, let us then consider another sign, this time one which is rare in the diagnosis of PD (but not rare in the other diagnostic categories). We will calculate $1 - p(\text{agnosia})$ for r_i with the following result: .0001, .0002, .0033, .000, .0015, .2450, .0007, .0031, .0043, .0504, .5173. $\tau = (.5173 - .2450) / (.5173 - .0001) = .5206$. There is a large increase in the value of tau using the symptom agnosia which is more than the critical value at 0.05 level and even more than the value at 0.01 (0.502). So, we can stop, reject the null hypothesis, and accept the alternative one. Four signs define an algorithmic rule for Parkinson's dementia: the presence of facial bradykinesia, limb bradykinesia and increased limb tone, and the absence of agnosia.

Results

Table 1 presents the matrix of actual frequencies of a selected group of symptoms and signs for the differential diagnoses of dementia. Based upon the methods described above, we derived from these frequencies a set of ten symptoms and signs which provided necessary and sufficient discrimination between the dementia diagnoses. These ten include signs from; i) the neurological examination: facial bradykinesia, limb bradykinesia, limb tone and focal signs; ii) the medical history and CAMDEX informant interview: a history of stroke, memory impairment, and a measure of activities of daily living; and iii) the cognitive examination: impaired abstract thinking, impaired judgement, and agnosia.

The comparison between the clinician and algorithm diagnoses is presented in Table 2. A total of 988 (87.3%) of the 1132 dementia cases were identified by our algorithm. Direct correspondence was not possible with respect to the three levels of severity in the clinician diagnoses of Alzheimer's disease and vascular dementia. In particular, the possible Alzheimer's diagnoses proved particularly difficult to pattern in accord with the clinicians' diagnoses.

The four algorithmic categories which incorporated some recognition of Alzheimer's disease were able to identify 83.5% of all clinical diagnoses of probable Alzheimer's disease (325 cases identified in algorithm as AD1, AD2, ADPk or mAVd divided by the 389 Probable Alzheimer's cases which contained adequate completed data). There was 77.7% consistency between the algorithm diagnoses of vascular dementia (mAVd, VD1, VD2) and the clinician vascular dementia and Possible AD with vascular components categories (240 cases identified in the algorithm compared to a total of 309 cases clinically diagnosed).

The algorithm identified 141 subjects with Alzheimerized vascular dementia (mAVd) compared to 137 study patients diagnosed with "mixed" AD/VaD (PA-vascular). The algorithm reassigned cases between the groups, particularly in VaD. Forty-four of a total of 208 subjects (21%) diagnosed with vascular dementia were reassigned by the algorithm to the Alzheimerized vascular dementia category (mAVd), compared with only 26 of 448 (6%) of probable Alzheimer's disease cases. Mixed AD-VaD subjects were commonly assigned to either VaD (53/137; 38%) or AD (33/137; 24%).

Parkinsonism was identified as a component in 31 Possible Alzheimer's cases and as Parkinson's disease in 26 cases during the clinical assessment. Our algorithm accounted for 36 of these cases (63.2%), but intriguingly placed 18 vascular dementia clinical diagnoses and 58 Probable and possible Alzheimer's cases into the categories of PD and ADPk.

Discussion

We identified distinct patterns in the estimation of probabilities of symptoms and signs in the differential diagnoses of dementia. The particular configuration of items which provided the best probability for that diagnostic category was incorporated into an algorithm, which was tested against clinical diagnosis. The algorithm identified 87.3 % of the dementia cases. The possible Alzheimer's diagnoses proved particularly difficult to pattern, analogous to the often complicated clinical presentations. Our algorithm identified four categories of probable Alzheimer's disease included an AD1 (mild) and AD2 (moderate and severe), an Alzheimerized Parkinson's dementia, a "mixed" Alzheimerized vascular dementia, and two stages of vascular dementia, VD1 and VD2.

As noted in our earlier paper, there are important caveats to secondary analysis. For example, not all the data which we might have wished was present. Additionally, even in a very large database, there are comparatively few cases to allow us to definitively address questions such as whether psychiatrists and neurologists use different coordinations of items in arriving at, say, a diagnosis of Parkinson's dementia. Thus much of our analysis must be seen to be exploratory, and it is likely that validation will have to rely on using such methods in other databases.

This novel approach raises many questions for further research. For example, an interesting result was the emergence of alternative (algorithmic) classifications of an Alzheimerized Parkinson's disease category (ADPk) and a mixed Alzheimerized vascular dementia classification. Further exploration might provide evidence in the former of a new diagnostic category, such as Lewy body dementia [30], which was not yet operationalized, and therefore remained unidentified, during the CSHA data collection period. The mixed Alzheimerized vascular category is of particular note given recent evidence suggesting a link between Alzheimer's disease and vascular dementia [40,41].

The ten symptoms and signs presented here are not intended to represent either an exhaustive or even an optimal list of possible configurations of symptoms and signs. We are proposing, instead, that the heuristic approach which we have described may allow a multiplicity of routes to the diagnosis - many different constellations of symptoms and signs available from the clinical assessment, the clinical history and course could each yield correct diagnoses. Analogously, we have demonstrated elsewhere [8] high inter-rater reliability across specialties in the diagnosis of dementia, although it is likely that different subspecialties vary in the way in which they arrive at their diagnosis. These symptoms and signs can be arranged in many configurations based upon their probabilities for each individual case and each diagnosis. There are some that "fit" the diagnosis given the state of understanding and other, seemingly anomalous, cases that do not, due to the limits of interpretation [42] - indeterminacy is a crucial factor. Thus, there are likely to be different configurations of symptoms and signs sufficient for the diagnostics. As noted, further insight on this question can be derived by comparing the established criteria purportedly used by clinicians with the frequency "certainties" that are collected and currently exist in any number of databases internationally.

The development of an algorithmic procedure becomes an important adjunct in testing the validity of diagnoses in large epidemiological databases. Importantly, it also has the potential to meet the challenges of existing and emerging criterion using large databases which might otherwise be viewed as obsolete. We believe, that rather than relying on dichotomous cut points in decision trees to summarize the differential diagnosis of dementia, our approach of analyzing patterns of probabilities of symptoms and signs within diagnostic categories more appropriately reflects clinical decision-making. Moreover, tracking cognitive decline may be better served by this continuous, probabilistic approach rather than a categorical model [43]. The categories of cognitive impairment and dementia identified by our analyses, which incorporate different stages of severity, may well provide us with the necessary elements to better interpret this dynamic and complex process.

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Table 1

Probability Matrix by diagnosis for patient having symptoms

	Mild AD	Mod AD	Sev AD	Atyp PA	Vasc PA	Park PA	Coex PA	Mild VaD	Mod VaD	Sev VaD	PD
arterial hypertension	.259	.230	.262	.406	.439	.214	.165	.531	.539	.661	.164
facial bradykinesia	.037	.038	.202	.030	.073	.655	.045	.061	.101	.368	.846
limb bradykinesia	.048	.058	.241	0.00	.100	.840	.107	.128	.125	.404	.826
muscle bulk	.062	.061	.335	.074	.280	.267	.247	.239	.284	.571	.375
clouding of consciousness	.171	.406	.490	.229	.385	.516	.296	.170	.333	.470	.346
limb incoordination	.037	.067	.134	.033	.226	.167	.221	.273	.327	.750	.222
episodes of agitation	.060	.197	.410	.125	.267	.414	.247	.122	.220	.473	.174
impaired abstract thinking	.741	.956	1.00	.750	.943	.964	.924	.687	.808	1.00	.920
agnosia	.067	.336	.871	.107	.426	.474	.355	.106	.232	.610	.125
aphasia	.470	.500	.843	.469	.623	.724	.568	.551	.677	.815	.583
apraxia	.356	.532	.884	.433	.576	.826	.537	.239	.369	.796	.500
impaired judgement	.474	.892	.995	.765	.850	.926	.849	.440	.617	.983	.750
focal signs	.118	.062	.099	.143	.545	.161	.165	.820	.831	.903	.269
gait abnormalities	.347	.328	.676	.393	.644	.867	.466	.735	.741	.905	.733
history of stroke	.035	.045	.058	0.00	.564	.071	.047	.796	.779	.891	.042
memory impairment	.938	.926	.943	.879	.983	.900	.927	.773	.871	.966	.800
mood disturbances	.234	.282	.287	.034	.349	.407	.359	.426	.467	.725	.348
impaired posture	.147	.164	.568	.241	.446	.667	.329	.439	.494	.875	.778
resting tremor	.081	.038	.121	.088	.060	.607	.087	.020	.037	.081	.075
diminished strength	.086	.067	.212	.097	.368	0.00	.165	.523	.612	.818	.300
increased limb tone	.071	.105	.521	.207	.364	.857	.239	.444	.508	.870	.846
increased neck tone	.036	.060	.373	.100	.206	.577	.090	.043	.124	.443	.500
action tremor	.049	.090	.060	.059	.074	.269	.079	.122	.090	.100	.182
voice abnormalities	.025	.039	.217	.030	.221	.400	.140	.196	.240	.559	.600
ADL disability	.145	.435	.919	.286	.686	.733	.526	.300	.694	.943	.769
IADL disability	.366	.767	.978	.656	.829	.741	.771	.426	.867	.879	.750

(I)ADL = (Instrumental) Activities of Daily Living

Table 2
Comparison between the clinician and algorithm diagnosis

	Algorithm Diagnosis										
	AD1	AD2	ADPk	mAVd	VD1	VD2	PD	Other	Identified	Lack Data	Total
Clinician Diagnosis											
AD-mild	56	6	1	11	0	2	1	4	81	5	86
AD- mod	77	35	5	8	1	6	1	23	156	7	163
AD -severe	23	77	19	7	1	6	8	11	152	47	199
PA-atypical	17	5	0	6	0	0	0	3	31	4	35
PA-vascular	18	12	3	23	10	43	0	2	111	26	137
PA-Park	4	4	6	4	0	1	11	1	31	0	31
PA -Coexist	34	19	2	12	1	2	1	8	79	19	98
VD-mild	2	0	0	19	13	11	2	2	49	2	51
VD-mod	6	1	0	19	11	38	5	3	83	2	85
VD-severe	0	0	1	6	6	41	10	2	66	6	72
PD	2	2	2	3	0	0	17	0	26	1	27
Other	18	5	1	7	1	3	3	7	47	7	52
Unclassified	30	2	4	16	2	7	6	11	78	18	96
Sub-total	287	168	44	141	46	160	65	77	988	144	1132
Total		626		185		206	65	77	988	144	1132