ORIGINAL ARTICLE

Neurologic Signs Predict Periventricular White Matter Lesions on MRI

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ABSTRACT: ***Objective:*** Periventricular white matter disease (PVWD) is associated with abnormalities on tests that involve complex cognitive processes, along with an increased risk of cerebrovascular events which are associated with significant morbidity in older patients. This study investigates whether the neurological examination can predict the presence of PVWD on magnetic resonance imaging (MRI). No prior studies have assessed whether the neurological examination can predict the presence of PVWD on MRI. ***Methods:*** A focused neurological examination was performed on a random selection of patients referred for a MRI of the brain. Staff neuroradiologists who were blinded to the results of the physical examination independently read the MRI scans. The MRI interpretations were divided into four categories based on the degree of PVWD: none, mild, moderate, severe. ***Results:*** Twenty-three subjects had some degree of PVWD, while 25 subjects had none. The total number of neurologic signs correlated significantly with the severity of PVWD even when adjusting for the effect of age (rho=0.67, p<0.001). Ninety-one percent of subjects with PVWD had three or more abnormal signs, while 76% of subjects without PVWD had fewer than three. Abnormalities with the three step motor sequencing and horizontal visual tracking tests were maximally predictive of PVWD. One or both of these tests were abnormal in 96% of subjects with PVWD, while 64% of subjects without PVWD had no problems with either test. ***Conclusion:*** Simple neurologic tests can predict the presence or absence of PVWD on MRI.

RÉSUMÉ: Des signes neurologiques prédisent les lésions périventriculaires de la substance blanche à l'imagerie parrésonance magnétique. ***Objectif***: La maladie périventriculaire de la substance blanche (MPVSB) est associée à des anomalies des épreuves qui impliquent des processus cognitifs complexes ainsi qu'un risque accru d'événements vasculaires cérébraux comportent une morbidité importante chez les patients âgés. Le but de cette étude était de déterminer si l'examen neurologique peut prédire la présence de MPVSB à l'imagerie par résonance magnétique (IRM), ce qu'aucune étude antérieure n'a évalué. ***Méthodes***: Un examen neurologique ciblé a été effectué chez des patients choisis au hasard, référés pour IRM cérébrale. Les neuroradiologistes du service interprétaient les examens de façon indépendante, à l'insu des résultats de l'examen physique. Les interprétations étaient divisées en quatre catégories, selon le degré de MPVSB: aucune, légère, modérée, sévère. ***Résultats***: Vingt-trois patients avaient une MPVSB, alors que 25 n'en avaient pas. La corrélation entre le nombre total de signes neurologiques et la sévérité de la MPVSB était au-delà du seuil de significativité, même après ajustement pour l'effet de l'âge (rho = 0,67; p < 0,001) . Quatre-vingt-dix pour cent des patients ayant une MPVSB avaient trois signes anormaux ou plus, alors que 76% des patients sans MPVSB en avaient moins de trois. Les épreuves qui prédisaient le mieux la MPVSB étaient le three step motor sequencing test et le horizontal visual tracking test. Un ou les deux tests étaient anormaux chez 96% des patients atteints de MPVSB, alors qu'ils étaient normaux chez 64% des patients sans MPVSB. ***Conclusion***: Des épreuves neurologiques simples peuvent prédire la présence ou l'absence de la MPVSB à l'IRM.

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Periventricular white matter disease (PVWD) correlates with abnormalities on neuropsychological tests that assess complex cognitive processes[1] and the severity of PVWD correlates with deficits in attention, visual recognition and cognitive speed.[2] In Alzheimer's disease, PVWD correlates with the severity of dementia.[3] Certain deficits found on language and memory tests can predict whether PVWD is present.[4]

No prior studies have assessed whether the neurological examination, in patients who lack focal or lateralizing signs, can predict the degree of PVWD seen on MRI. This study investigated the relationship between commonly tested

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"cortical" neurologic signs and the presence and severity of PVWD as seen on MRI. The term "cortical signs" was used by Jenkyn et al to characterize the tests they performed, correlating them with the Halstead-Reitan battery[5] and age.[6] Similar tests were utilized in this study and we retained the term, though we consider the signs to indicate subcortical dysfunction as well.

METHODS

From August 1997 to October 1997, 63 subjects (35 female, 28 males) who had MRI scanning of the brain at the Georgetown University Hospital were randomly selected without regard to the reason for the MRI in this blinded prospective study. Informed consent was obtained from all subjects.

Six subjects with lateralizing signs (i.e. unilateral grasp reflex) and nine patients with a history of surgical intervention secondary to malignancy or aneurysm were excluded. Forty-eight subjects without focal or lateralizing neurological symptoms or signs (21 males, 27 females) were included in the study. The mean age of the subjects was 52.1 years (range 10-90 years).

One of the authors (CB) performed a neurologic exam on all subjects prior to imaging. **The exam consisted of 17 neurologic signs (Table 1).** A detailed description of the following tests was described by Jenkyn et al:[5] nuchocephalic reflex, glabellar blink, horizontal visual tracking, snout reflex, suck reflex, grasp reflex, palmomental reflex, paratonia of arms and legs, impersistence of lateral gaze, impersistence of eye closure/tongue protrusion, extinction of double simultaneous stimulation, spelling "world" forwards and backwards. Luria[7] described the tests we used to detect abnormalities on three step motor sequencing and palm/fist alteration. Borkowski et al[8] described how to test word fluency.

All scans were performed on a Siemens Vision 1.5T system (Erlangen, Germany). Each subject had at a minimum T1 axial and sagittal, T2 and FLAIR axial sequences taken. The majority of subjects also received gadolinium contrast and had T1 in two planes along with axial and sagittal sequences.

The MRI scans were read by one of three staff neuroradiologists who were blinded to the results of the focused neurological exam. The severity of PVWD was used to assess the severity of leukoaraiosis. Periventricular white matter disease seen on MRI was divided into one of four categories based on a scale as follows: 1) no PVWD, 2) mild PVWD indicating the presence of small, punctate areas of hyperintensity, 3) moderate PVWD indicating the presence of a thin confluent lining of hyperintensity around the ventricles along with small, punctate foci, and 4) severe PVWD indicating the presence of large confluent areas of hyperintensity. The grading scale used is similar to one used by Ylikoski.[9]

Statistical analysis

A stepwise multiple regression analysis was used to determine which of the neurological signs contributed the most variance in predicting PVWD. All signs were included as independent variables. The severity of PVWD was the dependent variable. Age was used as a covariant. Signs which were determined in the multiple regression analysis to contribute to

Table 1: Neurologic tests used in this study

1. Nuchocephalic reflex	–	The shoulders of a patient whose eyes were closed were turned quickly to the left and right, while noting the position of the head.
2. Glabellar blink	–	The patient was instructed to look at a point across the room, while the forehead was tapped by the examiner 8-10 times while standing outside of the visual field.
3. Visual tracking	–	While keeping the head still, the patient was asked to follow the examiner's finger as it was moved between two extremes of horizontal gaze.
4. Snout reflex	–	The examiner pressed and withdrew the middle phalange of the index finger against the patient's closed lips.
5. Suck reflex	–	The examiner placed the knuckle of a flexed index finger between the patient's lips.
6. Grasp reflex	–	The examiner stroked each palmar surface of the patient's hands with and without distraction.
7. Palmomental reflex	–	The examiner firmly stroked each thenar eminence of the patient's hands with a thumbnail.
8. Paratonia of arms	–	The examiner held up an arm of the patient, then dropped the extremity.
9. Paratonia of legs	–	The examiner held up a leg of the patient, then dropped the extremity.
10. Lateral gaze impersistence	–	The patient was asked to look at the examiner's finger held at 45 degrees from the horizontal plane for 30 seconds.
11. Eye closure impersistence	–	Patients were asked to close their eyes for 10 seconds.
12. Tongue protusion impersistence	–	Patients were asked to stick out their tongues for 10 seconds.
13. Double simultaneous stimulation	–	The examiner touched the ipsilateral hand and cheek on patients who had closed their eyes, while being asked where they were being touched.
14. Spelling world	–	The patient was asked to spell world forwards and backwards.
15. Three step motor sequence	–	The patient was asked to perform three consecutive changes of the position of each hand: "fist-edge-palm".
16. Palm/fist alternating reciprocal	–	The patient was asked to change in an alternating fashion the position of each hand: "fist-palm".
17. Word fluency	–	The patient was asked to generate as many words they could think of that started with the letter F in 1 minute.

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Table 2: Magnetic resonance imaging data

Patient	Reason for MRI	MRI findings	PVWD
1	Elevated prolactin	Normal	None
2	Double vision	Mild PWVD	Mild
3	Right facial pain, rule out mass	Partially empty sella	Mild
4	Left critical middle cerebral artery stenosis	Subacute left MCAinfarct	Moderate
5	Fever of unkown origin	Normal	None
6	Altered mental status	Increased signal on T2 and FLAIR in right perisylvian area	None
7	Rule out vertebrobasilar insufficiency	Chronic infarcts in left thalamus, cerebellum bilaterally, cerebral peduncles bilaterally, subacute strokes in perisylvian areas bilaterally	Mild
8	Headaches	Normal	None
9	Cerebral hemorrhage	Chronic-subacute hemorrhage in R thalamus	Severe
10	Dementia	Mild involutional changes	None
11	History of seizures	Normal	None
12	Headaches, rule out mass	Bilateral punctate deep WM changes	Mild
13	Rule out optic neuropathy	Normal	None
14	Psychotic break	Normal	None
15	Transient ischemic attack workup	Involutional changes, subacute infarct in right posterior central gyrus	Mild
16	Transient ischemic attack workup	Normal	None
17	Mental status changes	Involutional changes	Mild
18	Stroke	Severe PVWD, white matter signal abnormalities in left basal ganglia and pons	Severe
19	Rule out ischemic attack	Prominent ventricles and sylvian fissures	Mild
20	Pituitary mass s/p bromocriptine treatment	Sellar mass 4.5x3.5x3.1 cm	Mild
21	Headaches, rule out breast cancer metastases	Diffuse enhancement of meninges with nodularity	None
22	s/p inverted papilloma removal from right sinus, right maxillectomy	Normal	None
23	Evaluate left orbit	8mmx10mm enhancing mass in left orbit	Mild
24	History of multiple sclerosis	Moderate PVWD	Moderate
25	Forgetfulness	Involutional changes	Moderate
26	Right mastoid pain, s/p right radical mastoidectomy	Normal	None
27	Headache	Involutional changes, empty sella	Moderate
28	Rule out optic nerve compression	Severe PVWD	Severe
29	Follow up after optic nerve swelling	Bilateral optic nerve enhancement right>left	None
30	Neurosarcoid	Normal	None
31	Headache and dizziness	Normal	None
32	Headaches	Normal	None
33	New onset seizure	Normal	None
34	Rule out occipital lesion	Normal	None
35	History of multiple sclerosis	Involutional changes	Mild
36	Stroke work up	Left thalamic lacune	None
37	History of multiple sclerosis	Mild PVWD	Mild
38	Headaches	Normal	None
39	Seizure work up	Normal	None
40	Rule out aneurysm	Normal	None
41	Brainstem meningioma	Large enhancing mass along clivus	Severe
42	Rule out stroke	Normal	None
43	History of multiple sclerosis	Severe PVWD	Severe
44	History of multiple sclerosis	Normal	None
45	History of sarcoid, look at orbits	None	Normal
46	Tremor	Mild PVWD	Mild
47	Rule out multiple sclerosis	Moderate PVWD	Moderate
48	Rule out multiple sclerosis	Mild PVWD	Mild

Periventricular white matter disease (PVWD)

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Table 3: PVWD severity vs. Neurologic signs

Abnormalitites	None	Mild	Moderate	Severe	Total
visual tracking	7	12	3	5	27
paratonia-arms	5	7	3	3	18
3 step motor seq.	2	7	2	5	16
glabellar blink	6	5	2	1	14
suck reflex	3	4	3	3	13
paratonia-legs	3	3	3	3	12
nuchocephalic	6	2	0	2	10
lat gaze impers.	2	2	2	4	10
palmomental reflex	4	4	1	1	10
word fluency	3	3	1	1	8
palm/fist alt.	1	2	0	2	5
snout reflex	0	2	3	0	5
Ext to double stim.	0	2	0	3	5
grasp reflex	0	0	2	2	4
“world” backwards	1	1	0	1	3
conjugate gaze	1	1	0	1	3
impers eyes/tongue	1	1	0	1	3
TOTAL	45	58	25	38	166

prediction of PVWD with statistical significance were subject to further analysis using Spearman Rho correlations. Cross-tabulations were performed to determine sensitivity and specificity.

Results

Patients were referred for a MRI of the brain for various reasons. (Table 2). The reasons for ordering MRIs were limited to information found on the requisition. The MRI scans revealed 25 subjects without PVWD and 23 subjects with PVWD. Of the 23 subjects with PVWD, 13 had mild PVWD, five had moderate PVWD, and five had severe PVWD. Thirteen of the subjects with PVWD had no other MRI abnormality. Ten subjects with PVWD also had evidence of one of the following findings on MRI: involutional changes (6), a clival mass (1), a sellar mass (1), an area of enhancement: meninges (1), optic nerve (1). Of the 25 patients without PVWD, three had evidence of one of the following findings on MRI: involutional changes (1), an area of enhancement: meninges (1), optic nerves (1). One subject (without PVWD) had been treated with risperidone for a psychotic episode and had many cortical signs. Refer to Table 2 for more detail.

The number of abnormal neurologic tests in relation to severity of PVWD is shown in Table 3. The group with PVWD had more abnormal signs than the group without PVWD. The total number of neurologic signs correlated significantly (rho=0.67, $p<0.001$) with the severity rating of PVWD even when controlling for the effect of age ($r=0.51$, $p<0.001$), but the correlation between age and PVWD severity was also significant (rho=0.54, $p<0.001$).

The four signs that occurred with the greatest frequency in this study were interrupted horizontal visual tracking, paratonia in the arms, inability to perform a three step motor sequencing test, and a persistent glabellar reflex. A stepwise multiple regression analysis revealed two signs maximally predictive of PVWD: an abnormal three step motor sequencing test and interrupted horizontal visual tracking. The predictive relationship between these two neurologic signs and PVWD severity was independent of age.

Ninety-six per cent of the subjects with PVWD had one or both of these signs, and 64% of those subjects without PVWD had neither of these signs. Thirty-six per cent of the subjects without PVWD had one of those signs, though none had both. All of the subjects with severe PVWD had abnormal three step motor sequencing and interrupted horizontal visual tracking (Table 4). With two abnormal signs, the sensitivity for identifying PVWD on MRI is 92%, the specificity is 100%, and the positive predictive value is 100%. The group with PVWD had more abnormal signs than the group without PVWD. Ninety-one percent of the subjects with PVWD had three or more abnormal tests, while 24% of the subjects without PVWD had three or more abnormal tests (Table 5). Jenkyn et al[5] correlated three or more cortical signs with abnormalities on the Halstead-Reitan neuropsychological test battery. Our findings are in agreement.

Table 4: PVWD severity vs. Neurologic signs

PVWD	Abnormal 3 step motor sequencing only	Abnormal visual tracking only	Both signs present	Neither sign present
none n=25	2 (8%)	7 (28%)	0 (0%)	16 (64%)
mild n=13	1 (8%)	6 (46%)	6 (46%)	0 (0%)
moderate n=5	1 (20%)	2 (40%)	1 (20%)	1 (20%)
severe n=5	0 (0%)	0 (0%)	5 (100%)	0 (0%)

Table 5: Neurologic signs predict PVWD

	No PVWD n=25	PVWD n=23	
#abnormal signs	48	129	p<0.01
#patients with abnormal 3 step motor sequencing	2 (8%)	14 (61%)	p<0.001
#patients with abnormal horizontal visual tracking	7 (28%)	20 (87%)	p<0.001
#patients with one or both* abnormal signs	9 (36%)	22 (96%)	p<0.001
#patients with both* abnormal signs	0 (0%)	12 (52%)	p<0.001
#patients with 3 or more abnormal signs	6 (24%)	21 (91%)	p<0.001

*abnormal 3 step motor sequencing and visual tracking

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Discussion

Hachinski et al[10] coined the term leukoaraiosis to characterize the PVWD that is so often seen on computed tomography and MRI, especially in older patients. The development of the FLAIR technique has vastly improved our ability to detect PVWD.[11]

There has been some difference of opinion concerning the clinical significance of PVWD.[12-16] It is associated with increasing age,[17] dementing disorders,[3] cardiovascular risk factors,[17,18] ischemic injury,[11] an increased risk of cerebrovascular events,[17,19] and a higher risk of death from such events in older patients.[20] Periventricular white matter disease is an independent risk factor for intracerebral hemorrhage in patients being anticoagulated.[21,22] Severe PVWD is a major predictive factor for pneumonia, falls and death in the elderly population.[23] Patients with PVWD, without focal or lateralized neurological signs or symptoms, often have incontinence, gait disorders, and difficulties carrying out activities of daily living.[24]

The presence of a combination of abnormal neurologic signs correlates with the presence and the severity of PVWD. Ninety-one percent of the subjects with PVWD had three or more abnormal signs from the battery of tests that was administered. In particular, the presence of either interrupted horizontal visual tracking and/or failing the three step motor sequencing test correctly classified 96% of subjects found to have PVWD. Although age contributed to this relationship, the correlation remained significant when age was eliminated as a variable.

Jenkyn et al[5] found that certain clinical signs such as the nuchocephalic reflex, persistent glabellar blink and the suck reflex are more predictive than others for identifying abnormalities on the Halstead-Reitan battery of neuro-psychological tests. These signs tend to increase in prevalence as individuals age[6] but cortical dysfunction increases with age as well.

Some have de-emphasized the importance of PVWD claiming that it exists to varying degrees in both normal and demented elderly individuals.[15,16] However, the findings from this study reinforce the concept that older subjects with PVWD are not normal.[9,15]

We found that two tests were especially sensitive as correlates of PVWD: visual tracking and three-step motor sequences. The reason for this is not obvious. Perhaps tests that require the participation of large cortical segments are especially affected by PVWD.

The correspondence of a structural change on MRI with a functional disturbance on neurological examination validates both the finding of PVWD on MRI and the neurological examination. Both abnormalities can be seen in younger individuals and neither is exclusively the result of aging. The correlation between MRI and clinical testing indicates that both PVWD and what some still regard as minor or soft neurologic signs are, independently, reliable indices of brain dysfunction. The sensitivity of having an abnormal three step motor sequencing test and interrupted horizontal tracking is 92%, and the specificity is high as well. No one without PVWD on MRI had both of these signs.

A brain MRI that does not reveal PVWD does not mean the brain is normal. For example, epileptics and patients on neuroleptics typically do not have PVWD or any other MRI abnormalities. The subjects examined in this study were suspected of having some form of brain disease, hence they were referred for the MRI. The subjects with cortical signs on physical examination whose MRIs were normal may well have had any number of cerebral disorders that MRI cannot detect. The battery of 17 neurologic tests may be quite sensitive for revealing problems with brain functioning, for no subject with PVWD was free of abnormal cortical signs. It was not practical to spend a full day performing the Halstead-Reitan battery on this population because it can cost more than a MRI of the brain, and takes an entire day to complete. However, Jenkyn et al[5] essentially used the same tests that were assessed in this study. They found a good correlation of cortical abnormalities with impairment on this neurological battery. The number of subjects in this study was small but the results encourage further investigation with a larger cohort into the relationship between findings on the neurological examination and findings on MRI scans.

Our finding that simple neurologic tests can predict the presence or absence of PVWD on MRI may have important clinical implications. The integration of the three step motor sequencing test and horizontal tracking adds approximately 20 seconds to a neurological examination. If patients have difficulty with these two tests, it is highly likely that they have some degree of PVWD. Even though PVWD is often present in older patients, these two tests could help prioritize patients who need a MRI of the brain. For example, a patient with abnormalities with these two tests in the setting of an otherwise nonfocal neurological examination may benefit from a MRI of the brain, since leukoaraiosis is associated with a higher risk of cerebrovascular events. Another situation in which a MRI may affect management is when a decision needs to be made regarding the initiation of anticoagulation, as leukoaraiosis is an independent risk factor for intracerebral hemorrhage.

The neurologic testing reported here is significant as proven by the correlation of three or more positive findings with MRI abnormalities. There is a strong correlation between abnormalities with the three step motor sequencing and horizontal tracking tests and the presence of PVWD on MRI. The fact that abnormalities on the neurologic exam are more prevalent amongst the aged also supports the significance of the findings, as neurologic impairment is more prevalent amongst the aged. Jenkyn et al[5] showed that findings that many still refer to as “soft” or “unreliable” correlated with abnormalities on the Halstead-Reitan Battery. The findings of Jenkyn et al[5] and our findings that correlate such signs with MRI abnormalities indicate that the neurological examination that we have performed reveals “hard” findings or reliable evidence of real neurologic impairment. Sometimes this impairment is the result of structural disease (leukoariosis), sometimes it is the result of a drug effect (risperidone). There are many other causes of frontal cortical and subcortical dysfunction. It is important to note that the neurological examination that can be performed at the bedside is one of several tests that can reveal the presence of neurologic dysfunction.

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