Primitive Reflexes in Alzheimer’s Disease and Vascular Dementia

Fred W. Vreeling, MD, PhD, Peter J. Houx, PhD, Jellemer Jolles, PhD, and Frans R.J. Verhey, MD, PhD

ABSTRACT

Data on the prevalence and clinical value of primitive reflexes (PRs) in dementia are controversial, mainly due to a lack of standardization of the methods by which these signs are elicited and scored. A standardized protocol was used to investigate eight PRs in 20 patients with Alzheimer’s disease (AD), 20 patients with vascular dementia (VD), and 20 control subjects for each group. Both patient groups showed considerably more PRs than the control groups. The prevalence of PRs was related to the severity of dementia. No single reflex or combination of PR pathognomonic for dementia could be distinguished. The PR profile of AD and VD patients were similar. (J Geriatr Psychiatry Neurol 1995; 8:111–117).

Demented patients may exhibit a number of reflexes that are also present in the earliest stages of ontogenetic development. These developmental or primitive reflexes (PRs), also referred to as release signs, are ubiquitously present in fetal life, in the newborn or infant, and gradually disappear with increasing age. They may reappear in senescence and with neurologic disease.

There have been claims that various PRs are strongly correlated with dementing conditions such as Alzheimer’s disease (AD), vascular dementia (VD), or dementia in Parkinson’s disease. Several authors have argued that (particular) PRs may be indicators of cognitive dysfunction, impaired ADL function and dysfunctional behavior. Diffuse hemispherical damage and focal lesions, notably of frontal areas, have also been mentioned in this respect. Some authors have found a correlation between the prevalence of PRs and cortical atrophy, whereas others have not. Recently, PRs were investigated in community-dwelling AD patients versus nondemented controls. Although PRs occurred with increased prevalence in the patients, they occurred too infrequently early in the course of AD to serve as diagnostic markers. In another study, release signs occurred in 55% of patients with AD, but they were also present in 9% of control subjects. Patients in a late stage of AD did not show a significantly increased prevalence of PRs compared with subjects in the early stage of AD. The conclusion was that these signs were neither sufficiently sensitive nor sufficiently specific to serve as a diagnostic marker for AD. Similar findings and conclusions were drawn in two other studies. However, it was recently found that when combined scores were made for various subgroups of reflexes, patients in a late stage of AD had a significantly increased prevalence of grasp, root, and suck reflexes (the prehensile signs) compared with control subjects and patients in an early stage of AD, who showed more glabellar, snout, and palmpalmtal reflexes (the nociceptive signs). Others question the clinical value of PR, considering the (re-)appearance of PRs as merely a sign of physiologic aging.

The potential contribution of PRs to the differential diagnosis of dementing conditions is unclear. This is because PRs are also prevalent among normal elderly people in other neurological diseases such as Parkinson’s disease, psychiatric disorders, and in nondemented patients with vascular abnormalities of the brain. PRs have been reported to predominate in VD with lacunae, especially in the frontal lobes, and in leuco-araiosis. The clinical value of PRs in distinguishing AD from VD could not be established by Marterer et al. They found no significant difference in prevalence of the glabellar tap and the grasp reflexes in patients with AD and multi-infarct dementia (MID). However, straightforward studies in which a “primitive reflex profile” (PRP) of AD and VD patients have been compared have not been performed up till now.

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Thus, the literature on PRs in dementing conditions is often controversial. This seems to be due to heterogeneity of the patient groups, a lack of compatibility between the methods used to elicit and score PRs, and the number of PRs studied.

The present paper investigates the prevalence of eight PRs in a group of community-dwelling AD and VD patients. The first aim of the study was to assess the effect of dementia on the prevalence of PRs, independent of the effect of aging. Because of the suggested relation between the prevalence of PR and the severity of dementia, cognitive functioning and the stage of dementia were also assessed. It is not yet known if PRs other than the glabellar or grasp reflexes or a PR will be useful in distinguishing between AD and VD. A clinical "primitive reflex profile" consisting of 8 PRs has not been studied in demented subjects. Recently, in our methodological study on PRs we found that application of a PR protocol, in which the instructions to the patient and the examiner, and the way of eliciting and scoring of the PRs are standardized, markedly increased inter- and intra-observer reliability.

The second aim was to determine the clinical value of these reflexes, by correlating them to parameters such as age and sex, severity of the disease, cognitive functioning, and depression. The third aim was to investigate if the PRF could be used to differentiate between AD and VD.

The reflex battery consisted of three categories of PRs. The first category consisted of reflexes often mentioned in relation to brain pathology in adults and/or in a brain aging perspective, namely the glabellar tap, palmomental, naso-labial, grasping, and sucking reflexes. The second category consisted of PRs that are not ubiquitously used, but which are mentioned in relation to brain pathology, namely the nuchoecephalic and pollicomental reflexes. The mouth open, finger spread reflex (MOFS) is used in child neurology and may have potential value in the assessment of adults.

The order in which the PRs are listed in 2A and 2B is in accordance with the proposals of Franssen et al (1982). Reflexes nos. 1 to 4 are "nociceptive" signs, reflexes nos. 5 and 6 are "prehensile" signs (the rooting reflex was not examined in this study), and the remaining reflexes, nos. 7 and 8, are categorized as "other" reflexes. The first group is termed nociceptive because each of them shows a facial contraction to a potentially noxious stimulus. The second category is termed prehensile because they seem to represent part of a prehensile syndrome (as described by de Ajuriaguerra), eventually evolving into paraplegia in flexion, described by Yakovlev.

**SUBJECTS AND METHODS**

We studied 40 community-dwelling patients with dementia enrolled at the Maastricht Memory Clinic, a specialized health care facility that is part of the Departments of Psychiatry and Neurology of the University Hospital in Maastricht, The Netherlands. Twenty patients (12 females; 8 males) with probable Alzheimer's disease and 20 patients (12 males; 8 females) with vascular dementia were studied. None of the patients received medication that could affect the ability to drive ("yellow sticker medication") and/or that could have a possible influence on consciousness.

Probable AD was diagnosed according to the NINCDS-ADRDA guidelines of McKhann et al. AD patients whose Hachinski ischemic score (HIS) was 4 or more were excluded from the AD study cohort. A HIS score above 7 was necessary for a diagnosis of VD. Most VD patients also had a history of hypertension and evidence of cerebrovascular disease on CT. Dementia was diagnosed according to the criteria of the DSM-III-R.

All patients underwent a thorough neurologic, neuropsychologic, and psychiatric examination, routine laboratory investigations, and a CT scan of the brain. The following rating scales were used: the Hamilton Depression Rating Scale (HDRS), Reisberg's Global Deterioration Scale (GDS), Blessed Dementia Scale (BDS), Hachinski Ischemic Score (HIS), and the Mini-Mental State Examination (MMSE).

Control subjects were matched to individual patients in the AD group and the VD group for age, sex, and level of education. They underwent a routine physical and neurologic examination and a neuropsychologic investigation. All control subjects were healthy and normal according to current criteria in gerontological research.

The characteristics of patients and controls are given in Table 1. VD patients were more demented than AD patients.

A battery of eight primitive reflexes (BPRs) was used to examine patients and controls. All reflexes were scored semiquantitatively in a two-cipher score for amplitude and persistence, as proposed by other investigators of PR in adults and in children. This is in accordance with the literature. A detailed description of the grading system is published elsewhere. The snout reflex is described in Table 2 as an example.

**RESULTS**

Figure 1 shows the mean number of positive responses, in patient and control groups, for all PRs as well as three reflex subcategories.

The overall number of PRs in both patient groups was higher than in the controls. There were more PRs per patient in the VD group than in the AD group, although this difference was not significant. Individual reflexes were detected more often in the VD group than in the AD group, except for the left grasp (equal) and the nuchoecephalic reflexes, which occurred slightly more frequently in the AD group. The average number of PRs per subject was 4.0 for AD and 5.8 for VD patients, and in their control groups, 1.6 and 1.4, respectively. The combined scores
Table 1. Characteristics of Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer's disease</th>
<th>Vascular dementia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>73.8 (5.5)</td>
<td>73.6 (5.7)</td>
</tr>
<tr>
<td>Age: range</td>
<td>84-83</td>
<td>62-83</td>
</tr>
<tr>
<td>Education: mean (SD)</td>
<td>3.2 (1.0)</td>
<td>3.6 (1.2)</td>
</tr>
<tr>
<td>Sex</td>
<td>8M/12F</td>
<td>8M/12F</td>
</tr>
<tr>
<td>HIS</td>
<td>2.4 (1.5)</td>
<td>—</td>
</tr>
<tr>
<td>BDS</td>
<td>7.3 (3.5)</td>
<td>—</td>
</tr>
<tr>
<td>GDS</td>
<td>4.6 (0.7)</td>
<td>—</td>
</tr>
<tr>
<td>MMSE</td>
<td>18.0 (4.9)</td>
<td>—</td>
</tr>
<tr>
<td>HDRS</td>
<td>7.7 (4.2)</td>
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HIS = Hachinski Ischemic score; BDS = Braak's Dementia Scale; 
GDS = Global Deterioration Scale; MMSE = Mini-Mental State Examination; 
HDRS = Hamilton Depression Rating Scale.

for the nociceptive reflexes were 2.4 for AD and significantly higher (P < .01) for VD: 4.3. For the control groups, these values were 0.9 and 1.1, respectively. The combined scores for the prehensile reflexes were 0.5 for AD and 0.6 for VD, and significantly less (0.1 and 0.0, respectively) for the controls (P < .05). The PR scores for the remaining reflexes were 1.2 for AD, and 1.0 for VD, and 0.6 and 0.3 for the respective control groups (both non-significant). The palmar grasp and right nocicephalic reflexes were not detected in the control groups. In these groups, correlations with age were observed: r = .48 for total PR, r = .46 for nociceptives reflexes in AD controls. For the VD controls these values were r = .46 and r = .45, respectively, all significant by t test (P < .05). In the AD and VD patients, these correlations were not significant.

Alzheimer’s disease

In the AD patients, 33%, and in the control group, 12% of all reflexes were positive. The difference between AD patients and their control subjects was particularly evident for the pallic- and palmamental reflexes, and to a lesser extent, for the suck, the nucocephalic, and the MOFS reflexes (see Figure 2A and B). This was in contrast to the findings for the glabellar tap and snout reflexes. The latter reflex was also present in relatively high frequency in the control group. The palmar grasp reflex was rarely found in the AD patients and was not present in the control subjects. There was only a small difference between the persistence of the PRs: in the AD group, 34% of the PRs persisted, but 25% persisted in the control group. There was no difference in the amplitude of the PRs between the patient and control groups: virtually all PR were weak to moderate. MMSE correlated well with age and BDS, as did GDS with BDS. There was, however, no correlation between these measures, the HDS, and the HIS on the one hand, and the total PR or one of the subgroups on the other hand.

Vascular dementia

In the VD patients, 60%, and in the control group, 11% of all reflexes were positive. There was a remarkably high prevalence of the pollicomental and the palmo-mental reflexes. The glabellar tap and the MOFS were also detected quite often in the VD patients. The snout reflex showed a high prevalence in both the patient and the control groups. The nucocephalic and the palmar grasp reflexes were infrequently elicited, but the suck reflex was present in one of three VD patients; these signs were not found in the control subjects. There was a slight difference in the persistence of the PRs: 57% and 45% of the PRs persisted in the VD and control groups, respectively (see Figure 3A and B). Again, virtually all responses showed a weak-to-moderate amplitude in both groups. GDS correlated with total PR, GDS, BDS, and MMSE correlated with prehensile signs. Nociceptive signs and total PR were strongly correlated; there was also a correlation between nociceptive signs and education. MMSE correlated well with education, BDS, and GDS. However, there was no correlation between HIS and PRs or any of the subgroups.
DISCUSSION

There was no indication of a basically different PR profile in the two patient groups, indicating that—at least in this stage of the disease—no reflex or combination of reflexes has a diagnostic value for differentiating between the dementing conditions. This is in accordance with the findings of Marterer et al.34

Franassen et al14 found significantly higher scores on summary variables that combined the scores of various individual neurologic measures, including PRs, already in nondemented subjects with mild memory impairment (GDS 3). The differences that are found in our series between the prevalence of total PRs, nociceptive, and prehensile signs in AD and VD patients and age-matched controls confirm their findings. The higher mean number of PRs and nociceptive signs in the VD compared to AD patients may be ascribed, in the first place, to the higher degree of dementia in the VD patients. Our findings are similar to those of Ishi et al,6 Steigart et al15 and Tweedy et al.63 In the review by Jenkyn and Reeves,64 several papers are mentioned in which PRs were found in diffuse cerebral dysfunction. Whether or not vascular etiology was prominent in these patient groups is not known.

A clear difference was observed for the prevalence of the prehensile reflexes between patients (AD and VD) and control subjects. The prehensile reflexes showed a relationship with CDS, BDS, and MMSE in the VD group, with the prevalence increasing with increasing severity of the disease. Franassen14 found that the nociceptive signs were more prevalent in the early stages of dementia, whereas the prevalence of prehensile signs increased sharply in GDS stages 6 and 7. Galasko et al5 found the grasp and Bakchine et al16 the grasp, suck, and snout reflexes associated with the degree of cognitive impairment in AD. No such relation was found for the palmmontal and glabellar tap reflexes. Finally, Molloy et al14 found no difference in the age or duration of AD in patients with and without PRs, nor was there any difference in cognitive function as measured with the MMSE, ADL, and IADL (Instrumental Abilities of Daily Living). Despite this, patients with PRs showed a greater degree of functional limitation and dysfunctional
behavior. Molloy suggested that the prevalence of PR could represent a clinical marker for a subgroup of AD patients with more severe impairment in ADL function. In the present study with community-dwelling patients, only 2 of the 20 AD patients and 5 of the 20VD patients were in stage 6. The numbers are small, so no definite conclusion can be drawn. However, our results support the strong indications that PR and cognitive deterioration are correlated. The data cast doubt on earlier suggestions that particular PRs might be of clinical value as indicators of the cerebral area involved.46,48-47 PR profiles should be applied to patients with well-circumscribed focal brain lesions.

As far as the individual reflexes, the glabellar blink was present in 21% of the AD patients and in 60% of the VD patients. Pearce49 reported that 72% of demented patients showed the reflex, whereas Koller50 found that 23% of AD patients and 8% of controls did. Other studies indicate that the glabellar blink reflex is among the most prominent release signs.22,69 Occasionally, we observed it in normal subjects with GDS stages 1 or 2; it was more prominent in GDS stages 3 to 6.4 The available evidence suggests that the glabellar blink is a release sign that develops quite early.

Similar conclusions apply to two other nociceptive reflexes: the palmo-mental and the palmo-mental reflex. The palmo-mental reflex is one of the first PRs to develop in adult life, according to Ajuriaguerra.14 Delwaide and Dijex5 confirmed this in a longitudinal study on AD patients. Various papers have shown that the palmo-mental reflex, as well as the palmo-mental reflex,53 which has been studied only infrequently, occurs with moderate frequency in nondemented elderly people and in the earlier stages of AD.41,12 Basavaranj et al54 found that only the palmo-mental and grasp reflexes could discriminate between demented and other neurologic patients. Recently, in a group comparison study on age-associated memory impairment (Vreeling et al, submitted for publication) it was shown that these two reflexes were present significantly more often in the patient group than in age-matched, healthy control subjects. Reis5 demonstrated that the palmo-mental reflex is present basically in all normal individuals, but the presence of a clinically evident reflex suggests a diminution of the cerebral inhibition on lower centers. McDonald55 found that variability in the palmo-mental reflex is related to the state of emotionality or anxiety of the subject. More studies are required to assess the relevance of these two reflexes in the elderly.

The snout reflex was found in 58% and 86% in AD patients and VD patients, respectively. However, almost half of the control subjects also showed this sign. Tweedy56 found a relationship between the snout reflex and cognitive decline. According to Koller,57 the snout reflex occurred with equal frequency in AD patients and in age-matched nondemented control subjects (54%); he also found that the snout was directly correlated with increasing age.

Gossman and Jacobs58 reported similar findings for Parkinson's patients and normal subjects. Hildenhagen59 showed that the snout reflex can be detected in up to 70% of subjects older than 80 years of age. Thus, the snout reflex, because of its sensitivity to the aging process per se, is not a good predictor of brain pathology.

The grasp reflex seemed to be highly specific for AD and VD in our patient series, since none of the controls showed the reflex. However, the sensitivity was extremely low: 10 and 15%, respectively. Tweedy53 found the sign in 17% of AD and in 14% of VD patients, and it was correlated with the cognitive score. Förstl44 and Huff442 found an increasing percentage of grasp reflexes (up to 34%) with increasing dementia. Girling60 observed the reflex in 8 of 24 demented 80-year-old people, and Bak- chine,10 who studied AD patients, correlated the reflex to a lower MMSE score. The conclusion is that if a grasp reflex is present and persistent, a hemispherical (frontal?) lesion is probable.

The suck reflex was found in one of three patients and in only two control subjects. As with the grasp reflex, Bakhchine50 found it correlated with the cognitive decline; however, both reflexes were rarely present (7.7% for the suck and 5.5% for the grasp reflex). Richard61 found this sign to be common in the second of three stages of AD. Again, if present it may indicate diffuse cerebral (frontal?) damage.

The rooting reflex, which was not examined in this study, is of interest in that other prehensile reflexes such as the suck and the grasp reflexes are detected, especially in more severely demented people.4 The PRs may develop in a particular order, with the rooting reflex developing after the suck and grasp reflexes. This interpretation is in line with the "retrogenesis" theory of de Ajuriaguerra and Hughlings Jackson (see above), and with the findings reported by Delwaide and Dijex52 in a longitudinal study of 104 patients with Alzheimer's disease. We plan to study the rooting reflex in future investigations.

Until now, the MOFS has been investigated almost exclusively in children.47,79,77 The prevalence in AD patients was about 40% and in VD patients even higher: 40% on the right side and 60% on the left side. These figures were about 20% for controls. As the pathogenesis and significance of the MOFS reflex are not yet clear, the high prevalence in the various groups motivates further research.

The muco-epithelial reflex was elicited in over 20% of our patients and in 4% of the controls. Jenkyn46 found this sign only rarely disinfibulated in normal adults, its presence increasing with age, and in patients with parkinsonism and cognitive impairment. It may serve as a nonspecific sign of diffuse hemispheric disease.

None of the eight reflexes tested has relevance as a possible pathognomonic sign of the disease. Instead, the data indicate that it is important to use combined scores, in which subgroups of PRs are formed to increase
the sensitivity of the measurement. This yields relevant data, even in the earlier stages of Alzheimer's and vascular dementia. A standardized PR protocol is essential in this respect. PRs, measured in a systematic way, may increase our insight into subtle brain dysfunctions that develop in adulthood and senescence.

**Future application.** PRs can be elicited throughout the course of AD and other dementias, including the end stage, when cognitive testing results in uniform low bottom scores. The change in type of PRs elicited during the early and late stages of AD might make PRs useful as independent markers of disease progression and as indicators of potential therapy. PRs could also be used in clinical practice and research to identify possible subgroups of AD, as was suggested by Molloy and Neary, because reliable categorization of AD patients in subgroups is currently only possible by histologic examination; simple clinical tests such as PRs could be helpful in this respect. However, Hansen found no difference in the prevalence of three PRs between two subgroups of AD patients with and without Lewy bodies. Finally, PRs might be useful in the differentiation of AD versus other dementing conditions such as depression.

**References**


