Neurological Soft Signs in Nursing Home Residents with Alzheimer’s Disease

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Abstract. Neurological soft signs (NSS), i.e., minor motor and sensory changes, are a common feature in psychiatric disorders related to brain changes. Nevertheless, they have rarely been investigated in patients with Alzheimer’s disease (AD). NSS were examined in 104 nursing home residents with AD with respect to dementia severity, neuropsychiatric symptoms, and Parkinsonian signs as well as potential medication effects. 16 cognitively unimpaired residents served as a control group. NSS scores were significantly higher in residents with AD and were associated with both severity of cognitive deficits and non-cognitive symptoms, in particular apathy, but neither with Parkinsonian signs nor with antipsychotic medication. Our results demonstrate that NSS increase with progression of AD and one may hypothesize that they are linked to degenerative cerebellar changes. NSS in AD are clinically significant and thus, besides other neurological symptoms, are to be considered in diagnostics and therapy.

Keywords: Alzheimer’s disease, antipsychotic medication, neurological soft signs, neuropsychiatric symptoms, Parkinsonian signs

INTRODUCTION

Neurological signs like aphasia, apraxia, and primitive reflexes [1,2] as well as Parkinsonian or extrapyramidal signs [2–5] are frequently described in the course of dementias, in particular Alzheimer’s disease (AD) and may appear even in the preclinical stage [6–9]. Furthermore, Parkinsonian signs in old age are also associated with the risk of cognitive decline and the development of AD [8,10,11]. However, most studies focused on extrapyramidal symptoms (EPS) or Parkinsonian features, particularly bradykinesia, limb rigidity, resting tremor or gait and balance disturbances [12], but did not consider other domains of neurological dysfunction.

Neurological soft signs (NSS) involve poor motor coordination, sensory perceptual changes, and difficulties in sequencing of complex motor tasks [13]. They are a common feature in psychiatric disorders related to brain changes, such as schizophrenia or bipolar disorders [14], but do not appear to be specific to a certain diagnostic group [15]. Numerous studies in patients with schizophrenia found NSS to be associated with psychopathological symptoms and cognitive deficits [13,16] rather than extrapyramidal side effects of antipsychotic medication. In first-hospitalized patients, increased NSS scores could even be demonstrated to herald an unfavorable, chronic course [17].

Mild Parkinsonian signs (MPS) comprise generally progressive neurological symptoms including gait and balance changes, rigidity, bradykinesia, and tremor in older people without known neurological disease and without distinct brain pathology. The definition of MPS is heterogeneous; several studies referred to the Unified Parkinson’s Disease Rating Scale with one or more items being present in mild or moderate degree [18]. Similar to the concept of mild cognitive impairment, MPS represent a spectrum from normal aging to a subclinical or preclinical disease process, particularly regarding AD or Parkinson’s disease. The underlying pathomechanisms, nevertheless, remain unclear; possible factors comprise a decline in dopaminergic nigros-
trial activity, neurodegenerative changes in basal ganglia or vascular pathology. Parkinsonian signs are very common among the elderly; their prevalence increases with age, and they are associated with worse physical and cognitive performance, depressive symptoms, and higher mortality [11,19]. Parkinsonian signs and motor dysfunction are also associated with mild cognitive impairment [6–9]; motor dysfunctions may predict the risk of cognitive decline [11] or of developing AD [8]. Moreover, subjects with mild cognitive impairment and mild extrapyramidal signs have a higher prevalence of psychopathological symptoms, such as apathy, anxiety, depression, and sleep disturbances [20].

In a follow-up study including 228 elderly individuals, Richards and coworkers reported that subjects with mild extrapyramidal signs (i.e., changes of speech and facial mobility, resting tremor, rigidity, posture, and bradykinesia) at baseline were significantly more likely to become demented, the ones with additional cognitive impairment being at the highest risk [21]. In patients with AD, extrapyramidal symptoms are more frequent than in healthy controls, even in the absence of antipsychotic treatment [5]. In a cross-sectional study involving 164 antipsychotic-naive patients with mild to moderate AD, the subjects with extrapyramidal signs (bradykinesia, abnormal gait, rigidity, and postural instability; tremors and oral-mandibular dyskinesias were least frequent) were significantly older and more cognitively impaired than those without the respective signs. Moreover, severity of extrapyramidal signs was related to functional decline [22].

Although there is clinical evidence for coordination and fine motor skills impairment besides EPS and Parkinsonian signs in the course of AD, NSS have rarely been investigated yet in these patients. In the present study, we therefore compared NSS scores between nursing home residents with AD and cognitively unimpaired residents. We hypothesized increased NSS scores in the patients to be associated with both cognitive impairment and non-cognitive psychopathological symptoms, but not with Parkinsonian signs. Moreover, NSS scores were hypothesized to be correlated with apathy as a psychopathological symptom sharing a psychomotor component, comparable to the association of NSS with negative symptoms in schizophrenia.

MATERIALS AND METHODS

Participants

120 residents from nursing homes in different areas in Germany with possible or probable AD according to NINCDS-ADRDA criteria [23] or without any evidence for dementia were included. The residents were classified in four groups according to presence and severity of dementia: no evidence for dementia (n = 16); mild (n = 20), moderate (n = 50); or severe dementia (n = 34). Particular care was taken to exclude subjects with preexisting severe psychiatric or neurological disorders, such as schizophrenia or Parkinson’s disease, or with other forms of dementias, in particular Lewy body dementia. Patients in advanced stages of dementia who were unable to understand or follow simple instructions were also excluded. Various demographic and disease-related features, such as age, sex, or duration of stay in the nursing home were carefully recorded. In a sub-sample of 68 residents, the regularly applied medication was also assessed. The study was approved by the ethical board of the Heidelberg University, Germany. After complete description of the study to the subjects and/or their legal representatives, written informed consent was obtained prior to the investigation. Participants underwent a thorough clinical examination carried out by experienced geriatric psychiatrists including neurological and psychopathological status. Parkinsonian signs (rigor and tremor) were rated as ‘present’ or ‘not present’. Akinetic rigidity was not considered as its assessment requires the patient to walk, which was often not possible for the demented in advanced stages of the disease.

Psychometric measures

Global impairment and severity of cognitive deficits were assessed on the Global Deterioration Scale (GDS) [24] and the Mini Mental State Examination (MMSE) [25], respectively. Neuropsychiatric symptoms in general and apathy in particular were evaluated on the Neuropsychiatric Inventory (NPI) [26] and on the Apathy Evaluation Scale [27,28].

Neurological soft signs

NSS were assessed by using an adapted version of the Heidelberg Neurological Soft Signs Scale [13] including the items finger-to-nose movement, dysdiadochokinesia, pronation and supination, finger-thumb opposition, and mirror movements. Each item was scored 0 (no prevalence) to 3 (marked prevalence), leading to a maximum total score of 18. The items were selected from the original scale based upon our clinical and research experience with demented patients. Items should not be too complex, easy to demonstrate, and
**Understanding even for severely demented residents.** In addition, items that required walking were excluded to minimize the impact of severe physical conditions, such as gonarthrosis.

**Statistical analysis**

In a first step, clinical characteristics were compared between subgroups by calculating analyses of variance (ANOVA) with post hoc Tukey HSD test, Bonferroni (Dunn) t-tests, or chi² tests where appropriate. The association of NSS and sociodemographic data, cognitive and non-cognitive symptoms was investigated by calculating Spearman rank correlation coefficients. To address potential medication effects, NSS scores obtained in patients receiving an antipsychotic medication were compared with those measured in patients who were antipsychotic-free. Similarly, NSS scores were compared between patients showing Parkinsonian signs and those without. Analyses were carried out using SAS 9.2.

**RESULTS**

A total of 120 nursing home residents participated in the study, 98 (82%) of them being female. The mean age was 85.1 years (SD = 6.4, range 68–98) and the residents had spent an average of 32.2 months (SD = 43.4, range 2–285) in the respective nursing home. The mean MMSE score was 13.3 (SD = 8.8, range 0–30), the mean GDS score was 4.3 (SD = 1.5, range 1–6), the mean total NPI score was 5.8 (SD = 3.8, range 0–48) and the mean total AES score was 24.2 (SD = 14.4, range 0–54). Sample characteristics with respect to dementia severity are given in Table 1.

NSS scores were inversely correlated with MMSE scores (r = −0.38, p < 0.0001) (Fig. 1) and correlated with NPI total scores (r = 0.27, p < 0.005) and AES scores (r = 0.25, p < 0.05). Residents with AD showed significantly (p < 0.0001) higher NSS scores than the non-demented controls; within the patient group, NSS scores differed significantly between those with mild or moderate and severe AD, respectively (Fig. 2).

In contrast, NSS scores showed only minor, non-significant differences between patients without Parkinsonian symptoms and those with pronounced rigidity (5.7 ± 3.5 vs. 6.2 ± 3.7) or tremor (5.8 ± 3.6 vs. 6.0 ± 3.4), respectively.

In a sub-sample of 68 residents, a total of 39 (57%) received antipsychotic medication; 20 of them were treated with typical antipsychotics, 13 with atypical antipsychotics, and 6 received a combination of both. Comparison of NSS scores between patients who received typical antipsychotics with those obtained in patients who either received or not received atypical antipsychotics or were antipsychotic-free only yielded minor, non-significant differences (6.0 ± 3.4 vs. 5.9 ± 3.9, respectively). As to be expected, there was a significant association between antipsychotic treatment and rigor as well as tremor (p < 0.0001 each).

**DISCUSSION**

This study is among the first to systematically assess NSS in patients with AD and yielded three major findings: 1) NSS are significantly more frequent in patients with AD than in age matched controls; 2) NSS increase with progression of the disease and are correlated with both cognitive decline and non-cognitive symptoms in general and with apathy in particular; and 3) NSS are...
neither associated with antipsychotic medication nor with Parkinsonian signs such as rigor or tremor.

While most studies on NSS were conducted in patients with schizophrenia, studies concerning neurological features in AD concentrated on Parkinsonian signs and often failed to precisely define the impaired movement, making the results somewhat difficult to interpret [29]. Another important point is the feasibility of the respective clinical tests. Rigor and tremor can be also assessed in patients unable to walk or to stand. The assessment of akinesia as the third cardinal symptom of Parkinsonism is frequently rendered difficult since it requires the patient to walk – a prerequisite, which is often not met by the severely demented. Hypomimia is an important aspect of akinesia but cannot be reliably assessed in the presence of apathy. In our study, on the other hand, even severely demented and/or apathetic residents were able to perform the adapted version of the Heidelberg NSS Scale.

A variety of concepts and definitions of neurological
abnormalities in dementia, such as (mild) Parkinsonian signs, parkinsonism, or extrapyramidal symptoms, makes it difficult to compare the results. However, there is evidence that AD patients with extrapyramidal signs, particularly rigidity, bradykinesia, and tremor, represent a clinical subgroup with another clinical course and distinct neuropathological features that are not present in patients without Parkinsonian signs [30]. In a comparison of both patient groups, Burns and coworkers [31] found extrapyramidal abnormalities in AD to be associated with substantia nigra pathology including α-synuclein aggregation, hyperphosphorylated tau accumulation, and neuron loss. In a sample of 78 patients with AD and extrapyramidal signs, Hulette and coworkers [32] examined the neuropathological correlates of clinical parkinsonism and found concomitant Parkinson’s disease pathology with nigral degeneration and Lewy bodies in 20.5%. Gibb and colleagues [33] reported that mild degenerative changes accompanied by tangles in the substantia nigra and ventral tegmental area are common in AD, while severe cell loss is rare. The conclusion that Parkinsonian signs in AD are likely to be due to Lewy body pathology was recently corroborated by Haan et al. [34] who found a high specificity of Lewy bodies for extrapyramidal symptoms. Another potential cause for parkinsonism in AD is a loss of striatal dopamine transporter sites that is not simply the result of substantia nigra degeneration and hence differs from the mechanisms observed in Parkinson’s disease [35].

In contrast, NSS are correlated with distinct cerebral changes. In a voxel-based magnetic resonance imaging (MRI) study, Dazzan and colleagues [36] demonstrated that higher rates of NSS are associated with a reduction of inferior frontal gyrus, middle and superior temporal gyrus, and anterior cingulate gyrus in healthy individuals. Recent MRI studies investigated the association between NSS and neuroanatomical changes in schizophrenia [37]. They also found less severe NSS in first-degree relatives of schizophrenic patients, indicating that they are a marker for risk of schizophrenia [38]. NSS are also related to age of onset [39], severity and persistence of psychopathological symptoms, and poor social functioning [40]. A recent study of our group demonstrated that NSS in schizophrenic patients are associated with a decreased density in the pre- and post-central gyrus, pre-motor areas, inferior and middle frontal gyri, caudate nucleus, thalamus, and cerebellum [41]. These results are in accordance with previous studies describing volume losses in the basal ganglia, thalamus, and cerebellum [42,43], supporting the hypothesis of a disrupted cortico-cerebellar-thalamic-cortical circuit [41,44]. Studies using functional neuroimaging techniques reported a decreased activation of the sensorimotor cortices and the supplementary motor area [45,46]. In another study on drug-naive schizophrenic patients [47], only NSS indicating an impaired motor sequencing (fist-ring, fist-edge-palm, rhythm tapping production movements, and Ozeretski test) were found to be associated with total and regional gray matter losses involving prefrontal, posterior cingulate, temporal cortices, putamen, and cerebellum.

One may hypothesize that NSS in AD refer to mechanisms similar to the ones observed in schizophrenia, in particular with respect to cerebellar pathology. A considerable number of histopathological studies demonstrates that the cerebellum, a region widely rather neglected in AD research, undergoes degenerative changes [48–55]. A recent structural MRI study of our group revealed significantly decreased cerebellar volumes in AD patients when compared to healthy controls. This effect was associated with poorer cognitive performance [56], thus reflecting a degenerative process.

Our results demonstrate that NSS are correlated with non-cognitive symptoms, particularly apathy. Studies in schizophrenic patients report a correlation between NSS and psychopathology, particularly negative symptoms [40,57,58]. The question, however, whether the correlations between NSS and psychopathology in schizophrenia and AD correspond to common pathomechanisms awaits further clarification. It also remains unclear if NSS are a trait marker for the risk of developing AD; a recent study demonstrated that APOE ε4 carriers have significantly more NSS than non-carriers and that the presence of NSS is associated with higher age and lower MMSE scores [59].

Our study demonstrates that NSS are rather independent from Parkinsonian signs, the latter being significantly associated with antipsychotic treatment. These results underline that neurological features in AD are distinguishable with respect to their underlying cerebral pathology [60]. Parkinsonian signs are typically found in a subgroup of AD patients [30] and might be associated with the presence of Lewy bodies, substantia nigra pathology, or a loss of striatal dopamine transporter sites [31–35]. Additionally, Parkinsonian signs are frequently a side effect of antipsychotic treatment, which is reflected by the association of both factors in our study. In contrast, NSS appeared to be rather independent from antipsychotic medication.
Although special care was taken to exclude patients with neurological disorders or other dementias than AD, particularly Lewy body dementia, some patients in our study might be suffering from atypical or preclinical forms of those diseases that may have impact on neurological features. Moreover, it is often considered that vascular lesions are associated with NSS. While the present study did not include neuroimaging to exclude vascular changes, particular care was taken to clinically identify residents with coexisting vascular pathology as indicated by focal neurological signs or with history of stroke as well as patients with clinical evidence of other dementia subtypes than AD; those subjects were subsequently excluded.

From a clinical viewpoint, an accurate evaluation of neurological symptoms in dementia is crucial for diagnostic and therapeutic considerations. Patients showing Parkinsonian signs or NSS are at an increased risk of falls and falling injuries. Hence, NSS have to be recognized and identified as potential risk factors. In our study on AD patients, Parkinsonian signs appeared to be associated with antipsychotic treatment and are to be considered as potential side effects of the medication. NSS, in contrast, seem to have a distinct underlying pathology, which is poorly understood yet. Furthermore, it remains unclear whether NSS, similar to Parkinsonian signs, are of a predictive value for the development of AD in terms of a trait marker. Future studies may address this issue with respect to the underlying pathomechanisms, which may have further implication for early diagnosis and treatment.

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REFERENCES


