Potentially reversible dementias in a memory clinic population

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Summary

Introduction: Potentially reversible dementias are rarely detected in ambulatory care facilities. Actual reversibility is virtually not known and has been occasionally reported in the literature.

Aim: Our aim was to determine the prevalence of potentially reversible dementias among patients seen at the ambulatory care facility and to estimate their "real life" reversibility.

Subcjets and methods: A retrospective analysis of medical records of 258 outpatients attending the Memory Clinic of Central University Hospital of Lodz in the years 2002–2003.

Results: Potentially reversible dementia has been diagnosed in 18 (5 women, mean age 60.9 ± 4.9) subjects yielding 7% of all the subjects presented. These patients were significantly younger and the severity of their cognitive deficits was milder as compared to the "non-reversible" cases. Treatment was successful in only 3 cases, what translates into only 1.5% of the diagnosed as demented. Twenty seven cases with cognitive deficit but no dementia (depression or drugs side-effects) were claimed as potentially reversible and treated, in most cases (22 out of 27), successfully. However, within a 2 year period of follow-up, the development of dementia was observed in 13 of 22 cases.

Conclusions: Potentially reversible dementia is a rare phenomenon in ambulatory care facility. The majority of potentially reversible cases can be found among younger and less impaired patients. Even in cases treated successfully, the risk of developing dementia within 2 years is very high.

dementia / prevalence / treatment / reversibility

INTRODUCTION

The term "reversible dementia", that appeared in neuropsychiatric literature in the early seventies of the 20th century, was controversial from the very beginning. Its proponents suggested that the clinical use of the reversible dementia concept would diminish a detrimental diagnostic and therapeutic nihilism and, therefore, a long-term prognosis of many patients would improve as a result of diagnosing and curing treatable conditions. As a consequence of that way of thinking, several early dementia guidelines supported very comprehensive and expensive diagnostic workups aimed at detection of even quite rare conditions possibly influencing patients' cognitive status [1, 2, 3, 4, 5]. However, already in the eighties, serious doubts emerged on the prevalence rate of reversible dementias [6, 7, 8] and first clinical studies of a prognostic value of the concept have been published [9]. Attention was paid to a "real-life" reversibility, understood as situations of a detection of potentially reversible condition that once cured (or corrected), in fact influenced the patients' cognitive status. Such rate of "real-life reversibility" was significantly lower than reported in the earlier studies [6, 7, 10]. The necessity of an "all-in-

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clusive" diagnostic evaluation of every subject was questioned and patients' characteristics that should lead to a more aggressive workup were proposed for the first time [10]. Despite these uncertainties, the Quality Standards Subcommittee of the American Academy of Neurology in 1994 recommended a wide-range diagnostic workup, including neuroimaging for each subject evaluated [11].

Later studies supported a critical rather than enthusiastic attitude on the reversible dementia concept. Although, different abnormalities were detected relatively frequently in the cognitively impaired, an actual effectiveness of interventions was disappointingly low – approaching frequently only 1% of the studied cohorts [12, 13, 14, 15, 16].

With the advent of both ICD–10 and DSM IV systems, several diagnostic categories, previously classified as potentially reversible dementia, became the exclusion criteria for dementia. Therefore, depression (and its "cognitive dysfunction predominant" variants such as pseudodementia) and drug-induced cognitive impairment could not be classified as reversible dementias any longer. Some authors even proposed to suspend the use of the "reversible dementia" term or to change it to "potentially reversible cognitive impairment". Advocates of such terminological shift argue that, firstly, dementia cannot be reversible because it is *ex definitione* an effect of an irreversible and progressive brain disorder and, secondly, reversible deficits are usually clinically mild and often not fulfilling functional criterion of a dementia syndrome [14, 15, 16, 17].

Only few Polish papers in the field have been published to date, the majority of them focused either on associations between depression and dementia [18] or a significance of the reversible dementia construct in the differential diagnosis of the dementias [19, 20]. None of the abovementioned papers was, in fact, a research study.

In the present study, we retrospectively analyzed data from patients' medical files and attempted to answer two research questions:

1. What is the prevalence of stringently defined potentially reversible cognitive impairment (PRCI) in a population of a memory clinic? And,
2. What is the "real-life" reversibility, in other words, how many patients with a potentially reversible condition might actually benefit from a causative treatment in terms of cognition improvement?

SUBJECTS AND METHODS

The study was designed as a retrospective medical records analysis. A total number of 258 patients diagnosed and treated with memory complaints in a Memory Clinic of the Central University Hospital, Medical University of Lodz were included in the study. All patients were diagnosed with the use of standardized protocol that comprised structured interview (from both patient and a caregiver, if available), detailed psychiatric and neurological examinations and psychometric assessment aimed at cognitive impairment severity evaluation as well as its neuropsychological profile. Co-morbidities were screened with standard laboratory tests, including thyroid function (TSH) and vitamin B12 deficiency evaluations. The majority of patients (excluding those who were uncooperative or refused) also had at least one neuroimaging – usually computerized tomography. The clinical assessment protocol employed incorporates current recommendations of the American Academy of Neurology [21].

The dementia syndrome diagnosis was accepted once meeting requirements of the working criteria of the World Health Organization [22]. Specific disorders responsible for cognitive impairment and dementia were recognized according to the following criteria: ICD–10 – for dementia in Alzheimer's disease, mixed dementia in Alzheimer's disease, vascular dementia, dementia in Parkinson's disease, dementia in Creutzfeldt-Jacob's disease and dementia in Huntington's disease; Consortium on Dementia with Lewy Bodies – for dementia with Lewy bodies [23] and the consensus criteria for frontotemporal dementia [24].

Due to the retrospective nature of our study we established a minimal set of information required for the subject's record to be included in the study. Those included basic demographic characteristics, diagnosis according to predefined criteria, age at onset, severity of cognitive impairment evaluated with Clinical Dementia Rating Scale (CDR) [25] and, additionally the MMSE test score [26].

To be diagnosed as having PRCI, a patient, in addition to cognitive impairment needed to have a potentially reversible condition known to be associated with cognitive impairment or

dementia. PRCI diagnosis was always treated as provisional and longitudinally verified, including a response to causative treatment.

RESULTS

Among 258 initially recognized subjects, diagnosis of dementia was set in 195. Importantly, in agreement with ICD–10 criteria [22] patients with a depressive episode (N=15, 5.8% of the entire cohort) and those with drug-induced cognitive impairment (N=9; 3.5% of our cohort) were excluded from final analysis. Diagnosis of PRCI was stated in 18 subjects (5 women, mean age of 61±5 years) while dementia according to ICD–10 was diagnosed in 177 subjects (95 women, mean age of 74±9 years); a detailed analysis of diagnostic profiles and clinical-demographical correlates is reported elsewhere [27]. Thus PRCI comprised 9.2% of the group initially diagnosed as dementia and close to 7% of the entire cohort.

A comparison of demographic characteristics and dementia severity scores are shown in Tab. 1.

Patients with PRCI were significantly younger and less cognitively impaired (as documented by differences in MMSE and CDR) when compared with those with dementia. Moreover, in the PRCI group there were more men and these subjects were better educated, though the aforementioned differences did not reach statistical significance.

The most commonly recognized diagnosis in patients with PRCI were so-called neurosurgical (N=6; including 3 with normal pressure hydrocephalus, 2 with subdural haematoma and 1 with a tumour) and thyroid gland dysfunctions (N=5; 4 cases of hypothyroidism and 1 with hyperthyroidism); a whole range of diagnoses is presented in Tab. 2.

Cognitive status improvement was a relatively rare phenomenon. Only 2 (both with normal pressure hydrocephalus) of the 6 patients with neurosurgical diagnoses were qualified for surgery and only 1 improved clinically. Despite active hormonal therapy, no change in the cognitive status was observed in patients with thyroid dysfunctions. Notably, however, in 4 of 5 of them, an associated mood disorder was ameliorated. In both subjects with vitamin B12 deficiency (initial plasma levels of 19 and 34 pg/ml; levels above 200 were considered normal) the cognitive status partially improved. Unfortunately,

Table 1. A comparison of demographic characteristics of subjects with dementia (N=177) versus those with potentially reversible cognitive deficits (N=17)

Demographic variable or clinical characteristics	Subjects with dementia (N=177)	Subjects with potentially reversible cognitive deficit (N=18)	Statistical difference between the groups
Age (years)	73.9±9.2	60.9±4.9	t = 5.901 DF = 193 P < 0.0001
Gender (fraction of women)	0.537	0.278	χ^2 = 2.512 DF = 1 P = 0.1130
Years of formal education	7.5±6.7	9.9±7.0	t = 1.442 DF = 193 P = 0.1509
MMSE	17.6±5.8	21.0±3.9	t = 2.429 DF = 193 P = 0.0161
Dementia severity CDR (N)			
CDR=0.5	3	3	χ^2 (trend) = 18.594 DF= 1
CDR=1	59	12	P < 0.0001
CDR=2	80	3	
CDR=3	35	0	

Table 2. Clinical diagnoses among subjects with potentially reversible cognitive deficits

Diagnosis	Number of subjects	A rate per cent in the whole cohort studied (N=195)
Potentially reversible dementias – total	18	9.2
Thyroid gland dysfunctions	5	2.5
Idiopathic normal pressure hydrocephalus	3	1.5
Chronic heart failure	2	1
Chronic obstructive lung disease	2	1
Vitamin B12 deficiency	2	1
Subdural hematoma	2	1
Scleroderma	1	0.5
Metastatic brain tumor	1	0.5

the observed improvement was only temporary (about 6 months) and afterwards further dementia worsening was evident. In both cases diagnosis was verified longitudinally as atypical dementia of Alzheimer's type and cholinesterase inhibitors were used with partial success.

To summarize, out of 18 subjects recognized as having PRCI, partial and usually temporary improvement was seen only in 3 and the resulting "real-life" reversibility in the entire cohort was as low as 1.5%.

Subjects with depression and memory complaints (N=15) were evaluated separately. Interestingly, a clinical improvement (usually after SSRI's treatment) was seen in 12, most commonly in those whose previous medication were discontinued (typically low-potency neuroleptics like promazin or chloprotixen) or altered (usually from tricyclics). It must be, however, underlined that despite a relatively good short-term prognosis of such "pseudodemented" patients, after two years of observation, in 6 of 13 subjects being still taken care in our clinic the diagnosis was longitudinally verified as dementia (AD=4 and VaD=2).

Treatment effects of patients with drug-induced memory impairments varied significantly and were dependent on the type of drugs discontinued and time of taking them. Relatively mildly impaired patients due to typical neuroleptics, tricyclics and anticholinergics (all prescribed with no valid indications [like sleep disorder] or with not properly diagnosed disturbances labelled as psycho-organic syndrome,

vegetative neurosis or atherosclerosis), particularly those who took drugs shortly, improved significantly. However, in those taking benzodiazepines, opioid-like analgesics (tramadol) or using polypragmasia, no noteworthy improvements were seen.

Importantly, both the separately analyzed groups (depressed and drug-induced) were younger and less severely impaired as compared to those with dementia that alone might have been important in prognosis.

DISCUSSION

In the studied cohort of 258 subjects initially seen with memory complaints, potentially reversible conditions were seen in 42 (including depression and drug-induced disorders) which comprised 16.3%. This percentage is close to the result of a meta-analysis of studies published before 1988 (13.2%, depression included [6]) and to the results of later studies evaluating similar populations, where the reported rate of potentially reversible conditions varied between 16.5 and 26% [12, 13, 14, 28]. Also, the observation that only a subset of patients who have potentially reversible conditions are impaired to the extent that allows dementia syndrome diagnosis is in agreement with our results (in our cohort, it was 18 subjects, 7% of the entire group studied and 9.2% among those with dementia). The abovementioned percentages are similar to those reported in a meta-analysis of all the

data published between 1987 and 2002 [15]. Interestingly, depression and drug-induced disorders were predominantly seen in subjects with memory complaints but not dementia. This is in agreement with previous reports [14, 17, 28, 29, 30] and a meta-analysis [15].

Among the group of 42 subjects with memory complaints who were diagnosed as having a potentially reversible condition (with or without dementia) clinical improvement was evidenced in 20, of those 12 with depression, 5 with drug-induced disorders and only 3 in a clinically overt dementia syndrome. This result supports the importance of diagnosing and proper treatment of depression in patients with memory complaints. It also points at clinical implications of the unwise use of drugs in the elderly, particularly those having strong anticholinergic properties [14, 15, 17, 29]. At the same time, one must sadly affirm that the rate of improvement in subjects with a more severe cognitive impairment is very low, and, what makes the conclusion even worse, it usually is a temporary improvement [13, 15, 30, 31]. It clearly indicates the importance of early interventions in cases of cognitive impairment due to potentially reversible conditions [6, 15, 20]; otherwise, when intervention is late, the success rate might be close to zero [15, 29, 31].

Finally, one should note that there are several features helping at distinguishing subjects with potentially reversible memory impairment who would respond to treatment from non-responders. Amongst these features, apart from a mild level of cognitive impairment (and preferably no overt dementia), depression and detrimental effects of drugs, is also the short duration of impairment [13, 14, 17]. Prognosis gets poorer with the longer duration and in more severely impaired subjects, despite proper treatment measures [12, 14, 15, 29, 30, 31].

A comprehensive workup aimed at diagnosing potentially reversible conditions should then be proposed much more to patients with mild cognitive impairment and with a short history of impairment than to those with longer duration and higher severity of symptoms allowing a diagnosis of dementia. This conclusion is in sharp contrast, with a common practice of paying no attention to memory complaints (no dementia) of the elderly patients (by both family doctors and,

sadly, specialists), an *a priori* understanding them as associated with the ageing process and prescribing ineffective drugs (so-called pro-cognitive) [32] without precise diagnostic tests done.

CONCLUSIONS

Although potentially reversible conditions occur relatively commonly among patients with cognitive impairment, the actual reversibility rate of cognitive impairment after causal treatment is quite rare. The more severe impairment and the longer its duration, the smaller are the chances of reversal. Patients with milder forms of cognitive impairment (and preferably no overt dementia), those with depression or those whose cognitive deficit is due to undesirable drug-related effects (particularly anticholinergic) are the best targets for both aggressive diagnostic workups and possible specific treatments. In the light of our study as well as the critical literature review, any lags in diagnostic procedures and disregarding memory complaints (usually understood as part of inevitable ageing processes) need to be evaluated as both scientifically and ethically unjustified malpractices.

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