Mild impairments in cognition in patients with type 2 diabetes mellitus: the use of the concepts MCI and CIND

Type 2 diabetes mellitus (DM2) is associated with moderate cognitive impairment in verbal memory, mental flexibility, and information processing speed, while other cognitive functions remain relatively unaffected.[1] Moreover, epidemiological studies have shown that DM2 patients have a twofold increased risk of developing either vascular dementia or Alzheimer's disease.[1 2] In the present study we examined whether mild cognitive impairment (MCI) and ''cognitive impairment, no dementia'' (CIND)—two concepts that are used to describe cognitive impairment in the transitional state between normal aging and early dementia—can be applied to the cognitive impairments encountered in a population based sample of DM2 patients. Recently, these concepts have attracted considerable attention, as individuals who meet the criteria for either MCI or CIND are known to have a substantially increased risk of developing dementia.[3 4] MCI is defined as a memory deficit without impairments in other cognitive domains.[3] Patients with MCI develop Alzheimer's disease at an annual incidence of between 6% and 25%, compared with 0.2–3.9% in the general population of the same age. The broader concept of CIND is used to describe more general cognitive impairments, often encountered in relation to vascular risk factors. The diagnosis requires impairment in one or more cognitive domains and no dementia.[5] A fivefold increased risk of developing Alzheimer's disease, vascular dementia, or mixed Alzheimer/vascular dementia has been reported in patients with CIND.[4] If either of the concepts MCI or CIND is found to be useful in describing the cognitive problems in DM2, it may help identify DM2 patients who are at increased risk of developing dementia.

Participants were recruited for the Utrecht diabetic encephalopathy study, which assesses the impact of macrovascular and microvascular disease on cognition in DM2. This research was approved by the medical ethics committee of the University Medical Centre Utrecht. Patients (n = 90) were aged between 60 and 75 years, were known to have had DM2 for at least one year, and were recruited through their general practitioner. Age and education matched control participants (n = 40) were recruited through the patient (mostly spouses) (table 1). Exclusion criteria were a psychiatric or neurological disorder (unrelated to DM2) that could influence cognitive functioning, a history of alcohol or substance abuse, and dementia. All participants were functioning independently at home and had intact comprehension of the Dutch language. The participants had an extensive neuropsychological examination (11 tasks) addressing the following cognitive domains in both a verbal and a non-verbal form: abstract reasoning, memory, working memory, information processing speed, visuo-construction, attention, and mental flexibility.

Previous studies used variable case definitions of CIND and MCI, often based on the diagnostic opinion of experienced clinicians. We preferred a numerical approach, comparing test scores with available age and education adjusted normative data. This procedure results in an objective classification and facilitates comparison of different studies. Performance of the participants on each test was rated as either within the normal range (0), below average (1), or impaired (2). ''Normal performance'' was defined as performance between −1 SD and +1 SD from the normative mean, ''below average'' as between −1 SD and −1.65 SD from the normative mean (the lowest 16% of the normal population), and ''impaired'' as below −1.65 SD from the normative mean (the lowest 5% of the normal population). Performance on a cognitive domain as a whole was classified as impaired when the average rating of tests in that domain was >1.

Participants were classified as having CIND if they were impaired in one or more of the cognitive domains.[5] When memory was the only affected domain, the participant was also classified as having MCI, applying the Petersen criteria.[3] As a decrease in information processing speed is common in an elderly population, impairment in this domain had to be accompanied by a rating of 1 or 2 in more than half the tasks in another domain (average rating of tests in that domain >0.5) for the individual to be classified as CIND.

Overall, the number of tasks on which performance was impaired was higher in DM2 patients than in controls (patients: five tasks, interquartile range two to eight; controls: two tasks, interquartile range one to five; Mann–Whitney U test, $p<0.05$). The domains that were affected most often in both groups were mental flexibility (patients 11%; controls 10%) and information processing speed (patients 17%; controls 11%). Memory was relatively spared (patients 4%; controls 3%). Significantly more patients than controls met the criteria for CIND (χ^2 test, $p<0.05$; table 1). The proportion of participants classified as having MCI did not differ between the two groups. In addition, hypertension, major vascular events (excluding non-invalidating stroke), retinopathy, and neuropathy were more common in the DM2 patients (table 1). Within the DM2 group no significant differences were found between the patients with or without CIND for age, diabetes duration, HbA_{1c}, or any of the factors described above. The same applied for the controls with or without CIND.

Comment

The results show that DM2 patients overall had more cognitive impairments than control participants, predominantly affecting mental flexibility and information processing speed; these cognitive domains are known to be the most sensitive to cognitive decline associated with aging. The prevalence of MCI and CIND in the control group was comparable to previous population based studies.[3 5] CIND, but not MCI, was significantly more common in DM2 patients than in controls. Memory impairment, which is the main feature of MCI, was not the most prominent impairment in the DM2 patients. Rather, a more general pattern of cognitive impairment, affecting multiple domains, was observed. This pattern fits better within the broader concept of CIND. These results illustrate that,

Table 1 Characteristics of the participants and the number and relative frequencies of participants classified as having CIND or MCI

	DM2 patients (n = 90)	Controls (n = 40)	Statistics*
Demographic characteristics			
Age (years)	66.8 (5.5)	65.2 (4.5)	NS
Educational level (median, IQR)	4 (3 to 5)	4 (3 to 5)	NS
Male sex	47 (52%)	18 (45%)	NS
Estimated premorbid IQ	98.3 (16.9)	103.2 (15.2)	NS
Impaired cognitive function			
CIND	34 (38%)	8 (20%)	p<0.05
MCI	2 (2%)	0 (0)	NS
Medical characteristics			
DM2 duration (years)	9.6 (6.5)	–	NA
Treatment			
Diet	59 (65%)	–	NA
Oral medication	25 (28%)	–	NA
Insulin	6 (7%)	–	NA
HbA_{1c} (%)	7.0 (1.2)	5.5 (0.3)	p<0.05
Hypertension†	67 (74%)	14 (35%)	p<0.05
Non-invalidating stroke	5 (6%)	2 (5%)	NS
Other major vascular events‡	21 (23%)	3 (8%)	p<0.05
Retinopathy§	29 (32%)	0 (0)	p<0.05
Neuropathy¶	38 (42%)	7 (18%)	p<0.05
Depression**	5 (6%)	0 (0)	NS

Values are mean (SD) or n (%) unless specified.
*Between group comparisons for parametric data were done with *t* tests, for non-parametric data with the Mann–Whitney U test, and for proportions with χ^2 tests.
†Systolic pressure >160 mm Hg, diastolic pressure >95 mm Hg, or use of antihypertensive drug treatment.
‡Myocardial infarction and/or vascular surgery or endovascular intervention.
§Diabetic retinopathy severity scale as used in the Wisconsin epidemiological study of diabetic retinopathy, cut off score 1.5.
¶Toronto clinical neuropathy scoring system, cut off score 5.
**Beck depression inventory, cut off score 16.
CIND, cognitive impairment, no dementia; DM2, type 2 diabetes; IQ, intelligence quotient; IQR, interquartile range; MCI, mild cognitive impairment; NA, not applicable.

because of its focus on memory impairments, the concept of MCI should be used with caution outside the field of Alzheimer's disease research. The concept of CIND appears to be applicable more widely, but its current broad and non-specific definition remains a limitation. Thus the nature and magnitude of the cognitive impairments should also be taken into account when the classification of CIND is used. Future prospective studies, using clear criteria, should resolve whether the concept of CIND could serve to identify DM2 patients who are at increased risk of developing dementia.

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Excessive daytime sleepiness in migraine patients

Headache and sleep disorders are related in several ways. Sleep disorders occur in headache patients, headache is a common manifestation of sleep disorders, and secondary disorders may cause headache and sleep complaints. Excessive daytime sleepiness (EDS) or excessive somnolence is a common symptom, with a prevalence of 10–20% in the general population.[1]

EDS is a subjective feeling of a compelling need for sleep at unusual times and in abnormal environmental conditions. Sleep deprivation, sleep fragmentation, and hypoxia are believed to be the main mechanisms leading to EDS. EDS increases the risk of car accidents, causes health status and quality of life to deteriorate, and may increase mortality. EDS is associated with obstructive sleep apnoea syndrome, brain tumours, epilepsy, stroke, degenerative diseases, trauma, multiple sclerosis, and neuromuscular disorders.[1] The prevalence, mechanisms, impact, diagnosis, and treatment of EDS have never been assessed in migraine patients.

We studied 200 consecutive patients with chronic or episodic migraine diagnosed according to the second edition of the International Headache Society diagnostic criteria for migraine[2] from the Jefferson Headache Center, Philadelphia, USA . The Epworth sleepiness scale (ESS)[3] was applied to all patients and correlated with the diagnosis of chronic/episodic migraine, age, sex, body mass index (BMI), and headache frequency. Questions on mental and physical fatigue, concentration, and memory problems were rated using a 1 to 5 scale. The local ethics committee approved the study. EDS was defined as an ESS score of 10 or more.

Statistical analysis was done using the χ^2 and Fisher exact tests for proportions, and Spearman and Pearson's correlation tests. The level of significance was set at $p<0.05$.

Demographic data are given in table 1. Headache after dozing off was reported in 35% of all migraine patients (29% episodic, 40% chronic), and in 70% of patients with EDS. The chance of dozing off in a car was high in 1% of patients, moderate in 2%, and slight in 15%. The ESS correlated with mental fatigue, physical fatigue, concentration, and memory complaints ($p<0.05$), but did not correlate with BMI, age, or sex (NS). The mean (SD) ESS was 8.4 (4.3). An ESS score of 10 or more was present in 37% of all people with migraine, in 32.4% of those with episodic migraine, and in 39.8% of those with chronic migraine. A score of 15 or more was present in 10% of all migraine sufferers, in 15.3% of those with chronic migraine, and in 4.3% of those with episodic migraine ($p<0.05$; table 1).

Table 1 Demographic data and Epworth sleepiness scale in 200 patients with episodic and chronic migraine

Demographic data	
Age (years)	45 (12.5)
Sex (F/M)	162/38 (81%/19%)
BMI	27.8 (6.0)
Episodic migraine	72 (36%)
Chronic migraine	128 (64%)
Epworth sleepiness scale	
Mean (SD) score	8.4 (4.3)
Score 10 or more	
All migraine	37%
Episodic migraine	32.4%
Chronic migraine	39.8%*
Score 15 or more	
All migraine	10%
Episodic migraine	4.3%
Chronic migraine	15.3%†

Values are mean (SD) or n (%).
*NS; †$p<0.05$.
BMI, body mass index.

Comment

EDS is increasingly recognised as a significant public health problem.[1] It is common in migraine compared with the general population, with around a twofold increased prevalence in our migraineurs.

The risk of car accidents is assessed in other medical disorders based upon daytime sleepiness severity. Little attention has been paid to the risk of car accidents in migraine sufferers. EDS should be evaluated in this population because of the risk of accidents in those who report severe EDS.

EDS was correlated with fatigue in the migraine patients in our study. Fatigue has been reported in 85% of chronic migraine sufferers, and was found to be very common as a premonitory symptom in migraine.[4] Understanding the causes of EDS in migraine may shed light on the mechanisms of fatigue in these patients

Dozing off was recognised as a headache trigger in 35% of patients and in 70% of patients with EDS. EDS may aggravate migraine, and diagnosing and treating it may lead to better outcomes.

Sleep loss or inadequate sleeping time is the most common cause of EDS in the general population. Primary sleep disorders—such as sleep disordered breathing, restless legs syndrome, and periodic leg movements in sleep—are prevalent, particularly among older people and may contribute to EDS. Other medical conditions, such as cardiovascular and pulmonary diseases, psychiatric illness, chronic pain syndromes, and several neurological and neurodegenerative disorders, can disrupt sleep and lead to EDS. Moreover, drugs including diuretics, antihypertensives, sympathomimetic agents, corticosteroids, sedative-hypnotics, analgesics, and certain antidepressants can cause EDS by interfering with sleep continuity or by having a direct sedating effect in the daytime.[1]

Can migraine lead to EDS, is EDS the primary condition leading to migraine, or are migraine and EDS determined by different causes? All three possibilities may occur. First, EDS may be an accompanying symptom in migraine, and an increased EDS may be a result of having migraine; the frequency of migraine may also affect EDS, as our chronic migraineurs scored higher. Second, EDS may precipitate migraine attacks—in our study dozing off was reported to be a headache trigger in 35% of migraine patients and in 70% of those with EDS. Third, depression could be related to both migraine and EDS, because it is comorbid with migraine and can cause EDS. A control group and the evaluation of depression and anxiety symptoms would help to clarify the exact relation between EDS and migraine.

We previously hypothesised a hypothalamic involvement in chronic migraine.[5] The hypothalamus is potentially the mediator of EDS in migraine patients. Orexin, a recently described neuropeptide, is thought to play a role in the regulation of food intake, sleepiness, autonomic nervous system activity, and energy balance. Orexin containing cells are located in the lateral hypothalamus, with widespread projections to the entire