Hypoglycaemia and dementia in diabetic patients

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Abstract

Diabetes and dementia, which have a complex relationship between them, are undergoing extensive growth in their fields. The occurrence of hypoglycaemia, the potential severity of which has just been pointed out in some recent studies, must be included in these relationships. In fact, diabetes is the cause of decline in cognitive functions and most certainly is involved in the occurrence of vascular dementia. The brain, which is highly dependent on glucose for its metabolism, is particularly vulnerable to hypoglycaemia in children and the elderly. Animal studies and pathoanatomical observations confirm the clinical impression of the reality of genuine post-hypoglycaemic encephalopathy. The impact of mild hypoglycaemia however is being debated. Lastly, the existence of dementia promotes the occurrence of hypoglycaemia due to disorders related to eating habits or poor treatment management. This hypoglycaemic risk however must not constitute a pretext for exaggerated laxity in achieving the blood glucose objectives.

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Résumé

Hypoglycémies et démence chez le diabétiques

Le diabète et les démences dont les liens sont complexes, connaissent une expansion croissante. La survenue d’hypoglycémies dont certaines études récentes viennent de rappeler la gravité potentielle, doit être intégrée dans ces relations. En effet, le diabète est à l’origine d’un déclin des fonctions cognitives et participe très certainement à l’installation des démences vasculaires. Le cerveau qui dépend étroitement du glucose pour son métabolisme est particulièrement vulnérable aux hypoglycémies chez l’enfant et le vieillard. Les travaux menés chez l’animal et les constatations anatomo-pathologiques confirment l’impression clinique de la réalité de véritables encéphalopathies post-hypoglycémiques. Cependant, le retentissement des hypoglycémies mineures est discuté. Enfin, l’existence d’une démence favorise la survenue des hypoglycémies en raison de troubles du comportement alimentaire ou d’une mauvaise gestion du traitement. Ce risque hypoglycémique ne doit toutefois pas constituer un prétexte pour un laxisme exagéré dans les objectifs glycémiques.

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Mots clés : Démence ; Hypoglycémie ; Diabète ; Déficit cognitif ; Insuline ; Revue

1. Introduction

Hypoglycaemia is a phenomenon that is justifiably feared by diabetics, their families and doctors owing to the accidents and complications that it can induce. Recent studies such as ACCORD and VADT have only strengthened these concerns by showing an increased risk of mortality and cardiovascular accidents in groups that receive intensive treatment. At the same time, there is a growing incidence of hypoglycaemia [1, 2]. The cerebral consequences of severe hypoglycaemia have been less extensively explored than the cardiovascular complications of diabetes. The brain, however, is directly and rapidly affected by the decrease in blood glucose since its metabolism relies exclusively on glucose. The majority of diabetologists have already noticed major cognitive changes occurring with repeated and severe hypoglycaemia, constituting the classic “post-hypoglycaemic encephalopathy”.

Considering the increased prevalence of dementia and diabetes, the optimal treatment of which is the control of hypoglycaemia, a clarification of relationships between
these two entities is required after an analysis of the methodological difficulties and reporting of the experimental and clinical data.

2. Definition and prevalence of hypoglycaemia in diabetics

The definition of hypoglycaemia is based on biochemical and clinical criteria: blood glucose level less than 0.60 g/L with suggestive symptoms. So-called “severe” hypoglycaemia is that which requires help from a third person. This definition is not quite precise enough since many cases of hypoglycaemia go undetected, especially those that occur at night, so as a result it is difficult to record them and assess the consequences. Mild hypoglycaemia is very common in type 1 diabetics and is not always reported by patients. The rate of severe hypoglycaemia varies according to the type of diabetes, the blood glucose objectives and the treatment used. It is rarer in type 2 diabetes treated with insulin or sulfonylureas. On the other hand, hypoglycaemia induced by insulin secretors is often more serious due to its long duration of action in cases of renal failure, especially in elderly subjects. It is therefore difficult to compare the consequences of repeated hypoglycaemia in young type 1 diabetics with those of fragile elderly subjects with type 2 diabetes.

3. Difficulties in determining the role of hypoglycaemia in the occurrence of cognitive disorders and dementia

The study concerning the relationship between hypoglycaemia and dementia faces several difficulties.

3.1. Heterogeneity of hypoglycaemia

The cerebral consequences of hypoglycaemia probably depend on its intensity, duration and rate of occurrence. As this information is often missing in published studies, it is difficult to determine the role of hypoglycaemia in the occurrence of cognitive disorders.

3.2. The definition of cognitive deficits and dementia

The determination of cognitive deficits and the diagnosis of the type of dementia are not always easy. Thus the boundary between cognitive deficit, early dementia and encephalopathy is difficult to discern. Diabetologists are poorly trained in this practice, which emphasises the worth of collaboration with geriatricians. Moreover, the term “hypoglycaemic encephalopathy” seems to be more appropriate than the term “dementia”, which is usually associated with Alzheimer’s disease or with vascular dementia in elderly subjects who present different anatomical and histological lesions.

3.3. Responsibility of diabetes in the occurrence of dementia

The relationship between hypoglycaemia and cognitive disorders in diabetics does not appear to be simple, insofar as the influence of the diabetic disease itself, its duration and its degenerative complications interfere to a great extent [3]. Indeed, diabetes itself seems to be responsible for the occurrence of dementia and cognitive deficits, so as a result it is difficult to separate the responsibility of blood glucose control, cardiovascular complications and severe or repeated hypoglycaemia.

At this stage, some epidemiological data on dementia during diabetes should be mentioned. The large epidemiological studies emphasize the joint increase in the prevalence of diabetes and dementia. This phenomenon is largely related to the aging of the population. The projections thus made by WHO show that between 1995 and 2025, the adult population will increase by 11% in developed countries, and the number of type 2 diabetics will increase by 42% [4]. In a parallel manner, over 33% of women and 16% of men over the age of 65 years will develop dementia and have resulting total loss of autonomy [5]. The incidence of Alzheimer’s disease, which makes up 70% of dementia cases, has been assessed at 1.17% in France. Alzheimer’s disease affects 1.5% of people aged 65 to 70 years and 30% of subjects over the age of 90 years [6].

Although the influence of diabetes on cognitive functions was suggested by Miles over 80 years ago and a large number of studies have been done in this area since then, no consensus has emerged regarding the responsibility of diabetes in the development of dementia or the protector effect of optimal blood glucose control [7]. As a consequence, the exact role of hypoglycaemia therefore seems to be difficult to pinpoint.

3.4. Lack of reference studies

Lastly, a large reference study on this question is missing. The available results up to now have often been contradictory. The recent implementation of the GERODIAB study by the Diabeto-Geriatric francophone group plans on answering some of these questions [8].

4. From experimental data to pathoanatomical observations

Brain structures are very sensitive to hypoglycaemia since they rely almost exclusively on glucose for their metabolism [9]. This explains the significance of neuropsychological signs of acute hypoglycaemic incidents, regardless
of whether they originate from medication or are related to an insulinoma.

The medium to long-term effects of hypoglycaemic episodes have however been less well described due to the lack of a reference study, which would be difficult to conduct. Animal studies done on rats show the high level of fragility of the hippocampus to hypoglycaemia, this being a region that is vital to the function of memorisation. The observed lesions are similar to those induced by chronic ischemia or by acute stress such as hypoxia [10]. Severe hypoglycaemia thus leads to necrosis of the neurons in the hippocampus region but also in the regions of the cortex. On the other hand, rats that underwent repeated and moderate hypoglycaemia seemed to be largely protected from the consequences of severe hypoglycaemia due to cerebral preconditioning to the lack of glucose [11].

Identical lesions have been demonstrated in diabetics who died from hypoglycaemic comas, thus confirming the high sensitivity of these cerebral areas in humans to the lack of glucose [12]. Results obtained in insulin shock therapy show improvement of psychotic states in patients subjected to hypoglycaemic shocks. These results were even used to justify the use of such methods in Soviet-era dissidents who were classified as having “subclinical schizophrenia”. It is probable that the observed improvements were actually related to the lesions in cerebral areas sensitive to hypoglycaemia. Fortunately, these methods have now become part of history.

5. Contributions of clinical studies

Few follow-up studies of sufficient duration have been specifically interested in the cognitive consequences of repeated and severe hypoglycaemia in humans, whereas glucose is essential to proper neuron functioning. Admittedly, the assessment of cognitive function, which is routinely practiced by geriatricians, has still not become part of the normal diabetology work-up. The ENTRED study in particular does not contribute much in this domain [13].

5.1. Influence of diabetes and hypoglycaemia on cognitive decline

Epidemiological data show a correlation between the main cardiovascular risk factors and the decline of cognitive functions, although this does not include dementia. This is particularly true of arterial hypertension [14,15].

Brain performance appears to be sensitive to acute variations in blood glucose levels [16]. However, the role of chronic hypoglycaemia in cognitive functioning is still the subject of controversy, although it appears to be a real phenomenon [17]. The deterioration of cognitive functions in diabetics is correlated to the time since the diagnosis of the diabetes and blood glucose control [18,19]. Deterioration of cognitive function can appear very early, from the glucose intolerance stage, even before the diagnosis of diabetes is made [7,20]. Not everyone however accepts the idea of diabetes as a risk factor of cognitive decline. Other studies have not observed any significant differences in cognitive functioning between controls, subjects with glucose intolerance and those with diabetes after adjustment for confounding factors [21,22]. Lastly, improvement of blood glucose control improved cognitive functioning in a small series of elderly type 2 diabetics [23].

The influence of hypoglycaemia must therefore be assessed by taking into consideration these complex and controversial data, in which some studies conclude that hypoglycaemia is responsible for cognitive deficits [24] and others rule it out [25, 26].

Large studies published in 2008 showed excessive mortality of cardiovascular origin in the intensive arms of the ACCORD and VADT trials. This fact appears to be related to an increase of severe hypoglycaemia [1,2,27]. On the other hand, although this is without a doubt due to the methodology and the limited duration of these studies, not enough emphasis has been put on the psychological consequences of hypoglycaemia. In the ADVANCE study however, the hypoglycaemic risk was low and there were no differences in cognitive changes between the two arms (intensive and conventional). Nevertheless, subjects that presented with cognitive disorders had an increased risk of death and cardiovascular accidents [28]. An ancillary study of ACCORD provided us with additional information, although it met with difficulties, since the glycaemic objectives in both arms were now identical. The specific aim of the ACCORD-MIND trial was to assess the influence of blood glucose control on cognitive functions. This transversal study shows that the increase of HbA1c is significantly related to decreased cognitive functioning as assessed by four validated tests [29]. It should be pointed out however that these results do not take into considerations the post-prandial blood glucose levels, which might contribute in the deterioration of cognitive functioning [30]. The ACCORD-MIND follow-up study, which is still underway, will provide data on the long-term consequences of blood glucose levels on cerebral performance.

This relative lack of scientific data contrasts with the fact that everyone is aware of the negative role of severe and repeated hypoglycaemia, particularly in type 1 diabetes, occurring in childhood.

5.2. Influence of diabetes and hypoglycaemia on dementia

Dementia is defined as the decline of memory and other cognitive functions over a given time period compared with the former state of the patient. Large post-mortem studies of elderly subjects with dementia showed that the dementia occurred in relation with Alzheimer’s disease in 80% of cases; the diagnosis of “pure” vascular dementia was present in 7 to 10% of cases; and a “mixed” dementia occurred in 3 to 5%, combining the lesions of Alzheimer’s disease and vascular
dementia. The role of hypoglycaemia turns out to be very modest in the usual aetiologies of dementia and its role in the appearance or worsening of dementia is difficult to clarify.

5.2.1. Alzheimer’s disease

Alzheimer’s disease is a degenerative disease of the central nervous system characterised by progressive and sustained weakening of all cognitive functions. Histologically it presents with specific neuropathological lesions. Hypercholesterolemia and systolic arterial hypertension seem to constitute independent risk factors of Alzheimer’s disease [31,32]. Diabetes might also be a risk factor for Alzheimer’s dementia, which would then place it in the vascular disease category rather than neurodegenerative [33]. This data is not only of theoretical interest, since the prevention and management of Alzheimer’s disease might be conditioned by those of cardiovascular risk factors [34]. Nevertheless, the type of treatment does not seem to influence the occurrence of Alzheimer’s disease [35]. The most recent studies agree that insulin resistance bears some responsibility for the occurrence of Alzheimer’s disease [36]. However, not all authors agree on the role of diabetes [37,38]. This fact was confirmed by a recent post-mortem study, which showed even that the lesions of Alzheimer’s disease are less frequent than in non-diabetics [39]. The role of hypoglycaemia thus seems to be very uncertain in early Alzheimer’s disease, the histological lesions of which are very distinctive. On the other hand, severe hypoglycaemia might worsen the cognitive disorders of Alzheimer’s disease.

5.2.2. Vascular dementia

Vascular dementia is characterised by a sudden deterioration of cognitive functions or by the occurrence of dementia within three months following a cerebral vascular episode [40]. In addition to this symptomatology, there must be focal neurological signs that are compatible with a cerebral vascular accident and anomalies on the medical imagery of multiple infarctions or hemorrhagic accidents. Diabetes increases the risk of occurrence of cerebral vascular accidents and could therefore promote the development of vascular dementia. In the study by Hassing, diabetes doubled the risk of vascular dementia but not Alzheimer’s disease [38]. The conclusions of the Rotterdam Study point in this direction: the presence of diabetes doubled the risk of the appearance of vascular dementia in 6370 elderly subjects who were initially free of dementia [41]. In a study of more than 1700 subjects over the age of 60 years, the combination of type 2 diabetes and cerebral vascular accident increased the risk of dementia by 8-fold [42]. Lastly, the combination of arterial hypertension and diabetes increased the risk of vascular dementia by 6-fold in a cohort of 1259 subjects who had been followed for seven years and were free of cognitive function alterations at the inclusion [43]. The results of these studies are thus often divergent, the role of hypoglycaemia is only rarely suggested and its responsibility in the occurrence of dementia becomes secondary.

6. Consequences of hypoglycaemia according to age and type of diabetes

The consequences of hypoglycaemia vary according to the type of diabetes and thus the treatment but also according to the individual characteristics. Indeed, the fragility of cerebral structures seems to be increased in children and elderly subjects.

6.1. Young subjects and type 1 diabetes

Type 1 diabetics, whose HbA1c target is below 7%, generally present with hypoglycaemia. As a result, there was a 3-fold increase in the risk of severe hypoglycaemia in the intensive arm of the Diabetes Control and Complications Trial (DCCT) [44]. The impact of these hypoglycaemic events must be assessed according to their severity, as well as their duration and frequency. The cerebral consequences have been well established and are a justifiable threat in children and in elderly subjects after deep and prolonged hypoglycaemic coma [45]. Severe and recurrent hypoglycaemia has an acknowledged negative effect on the cognitive abilities of diabetics, which can lead to hypoglycaemic encephalopathy [46]. This clinical picture is due to lesions of the frontal cortex and includes decreased cognitive functioning, particularly with regard to memory and attention, especially in children. Early-onset diabetes results in more significant disturbances of some cognitive and functional MRI tests [47]. In the DCCT study however, severe hypoglycaemia was not associated with decreased cognitive functioning, whereas some anomalies were observed in subjects with poor blood glucose control [48]. This hypoglycaemic encephalopathy therefore seems to mainly concern patients with early-onset (in childhood) type 1 diabetes that have presented with severe and recurrent hypoglycaemia. This clinical picture thus differs very considerably from signs of dementia both in its symptomatology and its cerebral lesions. The improvement of techniques and the quality of patient management of patients has most certainly limited the occurrence of these serious complications.

6.2. Elderly subjects and type 2 diabetes

The consequences of severe hypoglycaemia appear to be more significant in elderly subjects who generally present type 2 diabetes. Prevention of these metabolic incidents must therefore be included in a more comprehensive management of elderly diabetic patients, particularly with the aim of decreasing the frequency of falls, malnutrition and depression [49]. The incidence of hypoglycaemia induced by sulfonylureas is less common than those caused by insulin therapy, but they can
be longer lasting and therefore more serious, especially with pre-existing renal failure [50].

The medium and long-term consequences of hypoglycaemia are still being debated. Severe hypoglycaemia occurring between 55 and 65 years clearly seems to be a risk factor for the occurrence of dementia after 20 years of progression. In a large retrospective study on 16,667 elderly diabetic patients, the risk of occurrence of dementia increased by 26% in diabetics that had presented with one severe episode of hypoglycaemia, by 80% for two episodes of hypoglycaemia and by 94% for three or more episodes of hypoglycaemia [51]. The attributable risk of dementia between the subjects with or without a history of hypoglycaemia is 2.39% per year. Although this annual increase appears modest, the cumulative effect must not be neglected. On the other hand, the consequences of mild hypoglycaemia are not known [51]. This hypoglycaemic risk, especially in elderly subjects, must not however constitute an argument for laxity in the blood glucose objectives, which must be set individually according to the individual characteristics and the fragility of the patient [52].

7. Dementia promotes hypoglycaemic incidents in diabetics

Dementia alone is a significant risk factor for the occurrence of severe hypoglycaemia due to these patients’ random eating habits and errors in the management of their treatment [53]. In the ADVANCE study, an increase in the frequency of severe hypoglycaemia was observed in subjects presenting with significant cognitive disorders [28].

In the “Fremantle Diabetes Study” performed on 302 elderly diabetics aged over 70 years, there was a correlation between the history of severe hypoglycaemia and cognitive status. The existence of dementia was a very significant risk factor for the occurrence of severe hypoglycaemia in the 5 years following the study. On the other hand, there was no evidence of hypoglycaemia requiring the help of a third person in the appearance of cognitive deficits [53].

The recognition of the clinical manifestations of hypoglycaemia is difficult in patients presenting with dementia. In fact, agitation, increased confusion or other behavioural disorders may be associated with the dementia and lead to the initiation of inappropriate psychotropic drug treatment. For this reason, findings of a particularly low HbA1c level should cause suspicion of unobserved past hypoglycaemic episodes.

8. Conclusion

Severe hypoglycaemia has an impact on the function of the brain, which is highly dependent on glucose. Experimental data and post-mortem studies demonstrate significant alterations in brain tissue following severe hypoglycaemia. In daily practice, these severe hypoglycaemic events can induce genuine encephalopathy, especially in children or elderly subjects. The cerebral consequences however that might result from mild hypoglycaemia are not known. This missing information is due to the lack of fine assessment of cognitive functions in the therapeutic trials and the strong interference of the diabetic disease itself. The rate of severe hypoglycaemia has declined due to the improvement of techniques and therapeutic strategies, and the improvement of insulin and materials. Specific studies however on the relationships between diabetic hypoglycaemia and cognitive disorders must be conducted due to the growing prevalence of diabetes and dementia. Indeed, the risk of hypoglycaemia must not be an insurmountable obstacle to the optimisation of blood glucose control. The follow-up of the elderly diabetic cohort (GERODIAB study) implemented by the SFD-SFGG Diabetic-Geriatric francophone intergroup should be able to provide some responses to certain questions [8].

9. Conflict of interest

The authors have not declared any conflicts of interest

References


