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Frequency of brain ventricular enlargement among patients with diabetes mellitus

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ABSTRACT

Aims: To determine the prevalence of dilated ventricles and concomitant high blood glucose measures.
Methods: We retrieved blood glucose measures from the emergency department database and selected a subgroup of individuals having both the radiological marker Evans' index (EI) values and blood glucose measures.
Results: Out of 1221 consecutive patients submitted to axial Computed Tomography scans, a blood glucose measure was detected in 841 individuals. 176 scans (21 %) showed an EI > 0.30. According to the blood glucose categorization, diabetic patients were 104 (12 %), 25 of them (24 %) were dilated (mean EI 0.33). The age difference between dilated and not-dilated ventricles is about ten years in not-diabetic participants, whereas it is five years in diabetic participants. The age difference between dilated and not-dilated ventricles is about 10 years in diabetic men, whereas it zero in diabetic women.
Conclusions: Pathological ventricular enlargement is more frequent in men and in the elderly. In diabetic patients (especially women), the cerebral ventricles enlarge faster than in non-diabetic individuals. Age, sex, and diabetes may interact in determining how cerebral ventricle size changes over time, especially in diabetic women, making routine brain imaging advisable in these patients after the age of 70 years.

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1. Introduction

Some decades have passed from the first study highlighting a relationship between abnormal ventricular enlargement in the brain and diabetes mellitus.[1] Remarkably, in that series of 33 patients diagnosed as having idiopathic normal pressure hydrocephalus (iNPH) on the basis of clinical features and pneumoencephalography findings, the author reported that more than half of patients had diabetes (average 2-hour glucose level of 233 vs. 197 mg/dl in randomly selected normal controls).

Since then, interest in the frequency of diabetes mellitus in iNPH declined, likely due to the difficulty to reliably diagnose iNPH. Nevertheless, subsequent studies on the risk factors in elderly people [2] and patients with iNPH confirmed diabetes as one of the most frequent comorbid disease,[3–7] and a recent systematic review has definitively established this association.[8].

Therefore, comorbidity of diabetes and iNPH is not trivial. Indeed, dysregulation of the hypothalamic-pituitary axis secondary to dysfunction of the hypothalamus, the pituitary gland, or the surrounding vasculature is credited to ultimately decrease GH/IGF-1, thereby causing diabetes mellitus [9,10]. Because during aging the brain ventricles enlarge following an abnormal consecutive geometric dilatation influenced by age and sex [11,12], in the case the ventricular dilatation affects the functionality of the hypothalamic-pituitary axis, then individuals with dilated ventricles may be at a greater risk for presenting with diabetes mellitus than those not-dilated.

In the present study, we analysed the prevalence of comorbid diabetes mellitus and ventricular enlargement in a consecutive cohort of individuals undergoing an emergency brain computerised tomography (CT) scan and concomitant blood glucose measure. After categorizing subjects as not-diabetic individuals (N), and diabetic patients (D), we compared the prevalence of ventricular enlargement in both groups and evaluated the frequency of having enlarged ventricular system based on glycemic values.

2. Materials and methods

From a previous retrospective, IRB-approved (ref. 3601 2015–03-26), review of head CT data aimed to distinguish normal ventricular system size in normal aging from abnormal ventricular enlargement (Evans' index $>$ 0.30, i.e. hydrocephalus, Fig. 1) [11], we assessed subjects having concomitant CT scan and blood glucose measure. Neuroimaging measures taken from scans have been matched with the blood glucose levels (mg/dl).

Due to inhomogeneous clinical information on participants, and based on the real-world assumption that no patient can have a blood sample taken in the emergency department earlier than 1-hour from the clinical event, to maintain strict selection criteria, individuals have been subdivided into three categories: not-diabetic (**N**: 1-hour glycemia $<$ 121 mg/dl), **diabetic** (1-hour glycemia $\geq$ 181 mg/dl), not categorizable (120 mg/dl $<$ 1-hour glycemia $\leq$ 180 mg/dl). All subjects resulting with 1-hour glycemia $\geq$ 181 mg/dl were screened 4–6 weeks later to corroborate diabetes diagnosis.

All demographic and clinical data were subjected to descriptive analytics (i.e., age, sex, and frontal ventricular enlargement - evaluated by measuring the Evans' index). Categories were subjected to frequency and count analysis. Odds Ratio were calculated, logistic regression and ANOVA were performed where appropriate. Significance level was set at 0.05.

3. Results

Out of **1221** consecutive subjects undergoing axial CT scan in emergency department, a blood glucose measure was performed in 841 individuals, 436 women (52 %, aged 73 ± 13 years) and 405 men (48 %, aged 70 ± 12 years), who showed mean Evans' index values respectively of 0.27 and 0.28 (Table 1).

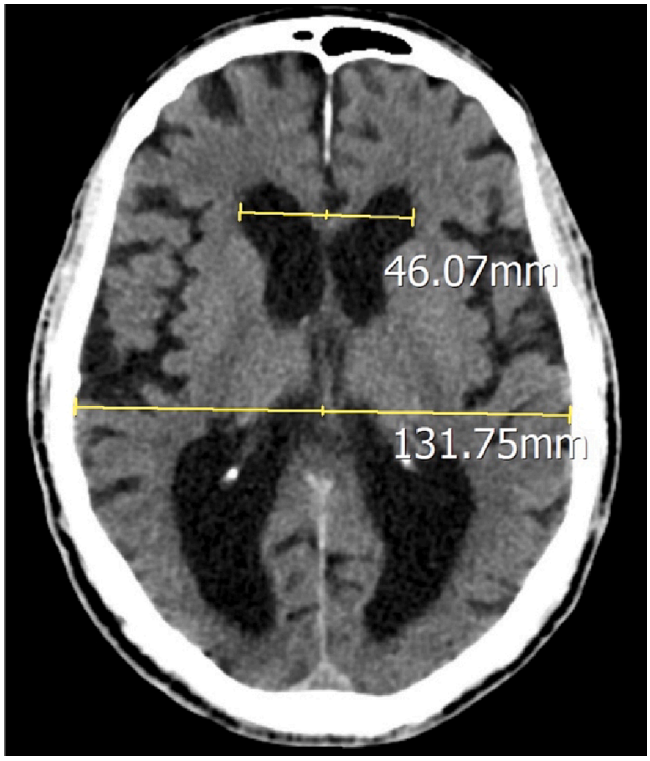

Fig. 1. Brain CT scan from an eighty-three-year-old man who had diabetes from age 50. Glycated haemoglobin (HbA1c): 74 mmol/mol (normal values 21–41). Following several falls the patient underwent a head CT scan, that showed enlarged ventricular system. By dividing the width of the frontal horns at the level of Monro's foramens by the maximum width of the inner table of the cranium (i.e., 46.07/131.75), the Evans' index value calculated as 0.34. After ventriculoperitoneal shunt, falls ceased, serum blood glucose decreased, and antidiabetic therapy could be reduced accordingly.

176 individuals (**21 %**) showed an Evans' index $>$ 0.30. According to the blood glucose categorization, **diabetic** patients were 104 (12 %), 25 of them (24 %) were dilated (mean Evans' index 0.33). All diabetic dilated patients 4–6 weeks later confirmed pathological glycemic values, corroborating the diabetes diagnosis. Not-diabetic subjects were 462**,** 86 (18.6 %) were dilated [(mean Evans' index 0.33), Odds Ratio 1.38].

In **not-diabetic not-dilated** individuals (n = 376), women prevailed [209 (55.6 %) vs. 167 (44.4 %) men], whereas in **not-diabetic dilated** individuals, men outnumbered women [50 (58.1 %) vs. 36 (41.9 %), Odds Ratio 1.74] (Table 2).

In **diabetic not-dilated** patients**,** men prevailed [51 (64.6 %) vs. 28 (35.4 %)], whereas in **diabetic dilated** patients gender difference decreased [13 (52 %) men vs. 12 (48 %) women; Odds Ratio 0.78].

Not-diabetic not-dilated patients had mean age of 68 ± 13 years, whereas **not-diabetic dilated** patients had mean age of 78 ± 8 years (one-way ANOVA, F = 51.14, p = 0.00) (Fig. 2).

Sex analysis shows that **not-diabetic not-dilated** men had mean age 66 ± 12 years, whereas **not-diabetic dilated** men had mean age 78 ± 8 years (one-way ANOVA, F = 40.92, p = 0.00) (Fig. 3).

Not-diabetic not-dilated women had mean age of 69 ± 13 years, whereas **not-diabetic dilated** women had mean age 79 ± 9 years (one-way ANOVA, F = 17.36, p = 0.00).

Diabetic not-dilated patients had mean age of 71 ± 11 years, whereas **diabetic dilated** patients had mean age of 76 ± 8 years (one-way ANOVA, F = 5.06, p = 0.03).

Sex analysis shows that **diabetic not-dilated** men had mean age 68 ± 11 years, whereas **diabetic dilated** men had mean age 77 ± 8 years (one-way ANOVA, F = 7.61, p = 0.01). In contrast, the mean age of

Table 1
All scans: demographic features and Evans' index (EI) in the various categories.

Study Group	N	Dilated n (%)	Age	Men n (%)	Women n (%)	Mean EI
All	1221	236 (19.3 %)	74 ± 14	565 (47 %) mean EI: 0.28 ± 0.04	656 (53.3 %) mean EI: 0.27 ± 0.04	0.27 ± 0.04
Dilated	236 out 1221	236 (100 %)	79 ± 9	121 (51.2 %) mean EI: 0.33 ± 0.03	115 (48.7 %) mean EI: 0.33 ± 0.02	0.33 ± 0.02
Having a blood glucose measure	841 out 1221	176 (20.9 %)	71 ± 12	405 (48.2 %) mean EI: 0.28 ± 0.04	436 (51.8 %) mean EI: 0.27 ± 0.04	0.28 ± 0.04
Not-diabetic (1-hour G < 121 mg/dl)	462	86 (18.6 %)	78 ± 8	217 (46.97 %) mean EI: 0.28 ± 0.04	245 (53.03 %) mean EI: 0.27 ± 0.04	0.27 ± 0.04
Diabetic (1-hour G > 180 mg/dl)	104	25 (24 %)	72 ± 11	64 (61.5 %) mean EI: 0.28 ± 0.03	40 (38.5 %) mean EI: 0.28 ± 0.04	0.28 ± 0.04
Not categorizable (120 mg/dl < 1-hour G<=180 mg/dl)	275	65 (24 %)	73 ± 12	124 (45 %) mean EI: 0.28 ± 0.05	151 (55 %) mean EI: 0.27 ± 0.04	0.28 ± 0.05

diabetic women did not change (76 ± 9 years) whether they were not-dilated or dilated (one-way ANOVA, F = 0.05, p = 0.87).

In **not-diabetic** individuals, a normal sized ventricular system turns in ventricular enlargement in approximately ten years (subjects' mean age when not-dilated 68 years, when dilated 78 years). This 10-year time span is halved in **diabetic** patients, in which the mean age of dilated vs. not-dilated is 71 vs. 76 years.

The linear regression analyses on continuous variables were performed on data from 841 individuals. Linear regression between age and EI values was significant (R-squared 0.162, p-value = 0.000); the same between sex and EI values (R-squared 0.013, p-value = 0.001). Linear regression between 1-hour glycemia values and EI values approached statistical significance (R-squared 0.004, p-value = 0.059).

Logistic regression between EI values (continuous variable) and 1-hour glycemia as binary dependent variable (<=120 mg/dl not diabetic patients; >180 mg/dl diabetic patients) performed on 566 individuals [obtained by summing "diabetic patients" (n = 462) and "not-diabetic patients" (n = 104), see Table 1], approached statistical significance (Odds ratio 205.659, p = 0.064).

Multiple logistic regression performed on 566 individuals with EI values as binary dependent variable (EI<=0.3 not-dilated, and EI > 0.3 dilated), 1-hour glycemia as binary independent variable (<=120 mg/dl not diabetic patients; >180 mg/dl diabetic patients), age as continuous independent variable, and sex as binary independent variable showed that older age (odds ratio = 1.082, p-value < 0.05) and being male (odds ratio = 1.810, p-value < 0.05) significantly influence ventricular enlargement, whereas 1-hour glycemia do not (odds ratio = 1.200, p-value = 0.505).

4. Discussion

By evaluating the Evans' index in this series of consecutive neuroimaging scans collected in an emergency department, we found a rate of ventricular enlargement slightly higher than that reported in normal population [13]. The increased rate determined here derives from at least two concurrent factors. One is an age-based selection bias that excluded scans from subjects younger than 45 years, who have notoriously normal-sized ventricles. Another is an emergency department-based enrolment that may have over-represented subjects prone to falls and minor head injury (thereby overrepresenting patients with iNPH).

We are aware that measuring ventricular volume is the best strategy for diagnosing ventricular enlargement. However, advanced neuroimaging techniques for ventricular volume measurement are time-consuming, require specialized software and expertise, and are not readily available in most resource-limited settings, thus proving unhelpful for routine quantitation of the ventricular size.

By assuming that individuals with 1-hour G > 181 mg/dl are diabetic patients for sure, our study showed a higher prevalence of diabetes in the present cohort than that reported in the general Italian population [14]. Again, most reasonably, this difference reflects an emergency department-based enrolment bias, that over-represents diabetics vs. not-diabetics individuals [15]. Concurrent over-representation of ventricular enlargement and diabetes likely renders the present study well-suited for studying comorbid diabetes mellitus and ventricular enlargement.

Taking together blood glucose measurements and Evans' index values, the present cohort of scans is in line with studies in patients with iNPH that identified diabetes as one of the most frequent comorbid diseases [3–8]. Although only marginally significant, the weak

Table 2
Demographic features and Evans' index (EI) in not-diabetic individuals and diabetic patients.

Study Group	**n (%)**	**Age**	**EI**	**Men n (%)**	**Men's EI**	**Men's age**	**Women n (%)**	**Women's EI**	**Women's age**
Not-diabetic not-dilated (1-hour G < 121 mg/dl; EI ≤ 0.30)	376 (81.4 %)	68 ± 13	0.26 ± 0.03	167 (44.4 %)	0.26 ± 0.03	66 ± 12	209 (55.6 %)	0.26 ± 0.03	69 ± 13
Not-diabetic dilated (1-hour G < 121 mg/dl; EI > 0.30)	86 (18.6 %)	78 ± 8	0.33 ± 0.02	50 (58.1 %)	0.33 ± 0.02	78 ± 8	36 (41.9 %)	0.33 ± 0.02	79 ± 9
Diabetic not-dilated (1-hour G > 180; EI ≤ 0.30)	79 (76 %)	71 ± 11	0.27 ± 0.03	51 (64.6 %)	0.27 ± 0.02	68 ± 11	28 (35.4 %)	0.26 ± 0.03	76 ± 9
Diabetic dilated (1-hour G > 180; EI > 0.30)	25 (24 %)	76 ± 8	0.33 ± 0.02	13 (52 %)	0.33 ± 0.03	77 ± 8	12 (48 %)	0.32 ± 0.01	76 ± 9

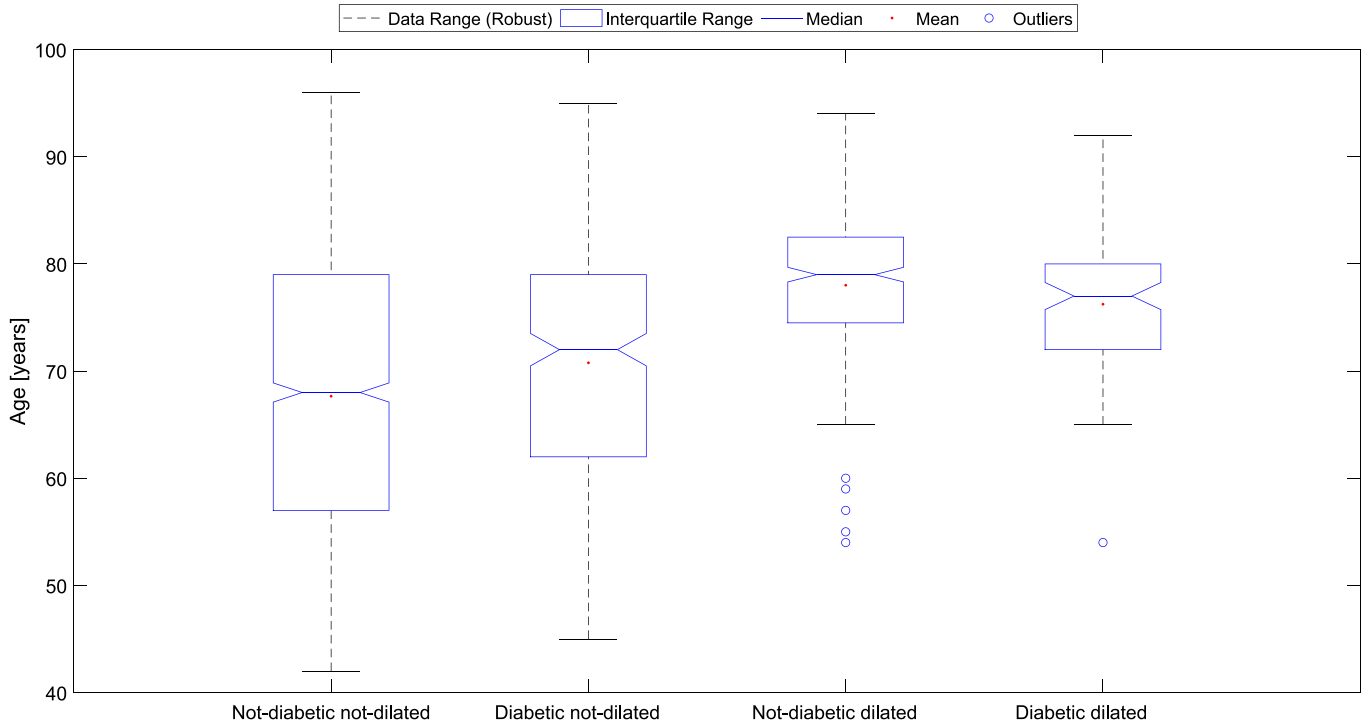

Fig. 2. Mean, median, interquartile ranges and outliers of age values in diabetic and not-diabetic participants having or not dilated cerebral ventricles. Please note that the age difference between dilated and not-dilated scans is about ten years in not-diabetic participants, whereas it is five years in diabetic participants.

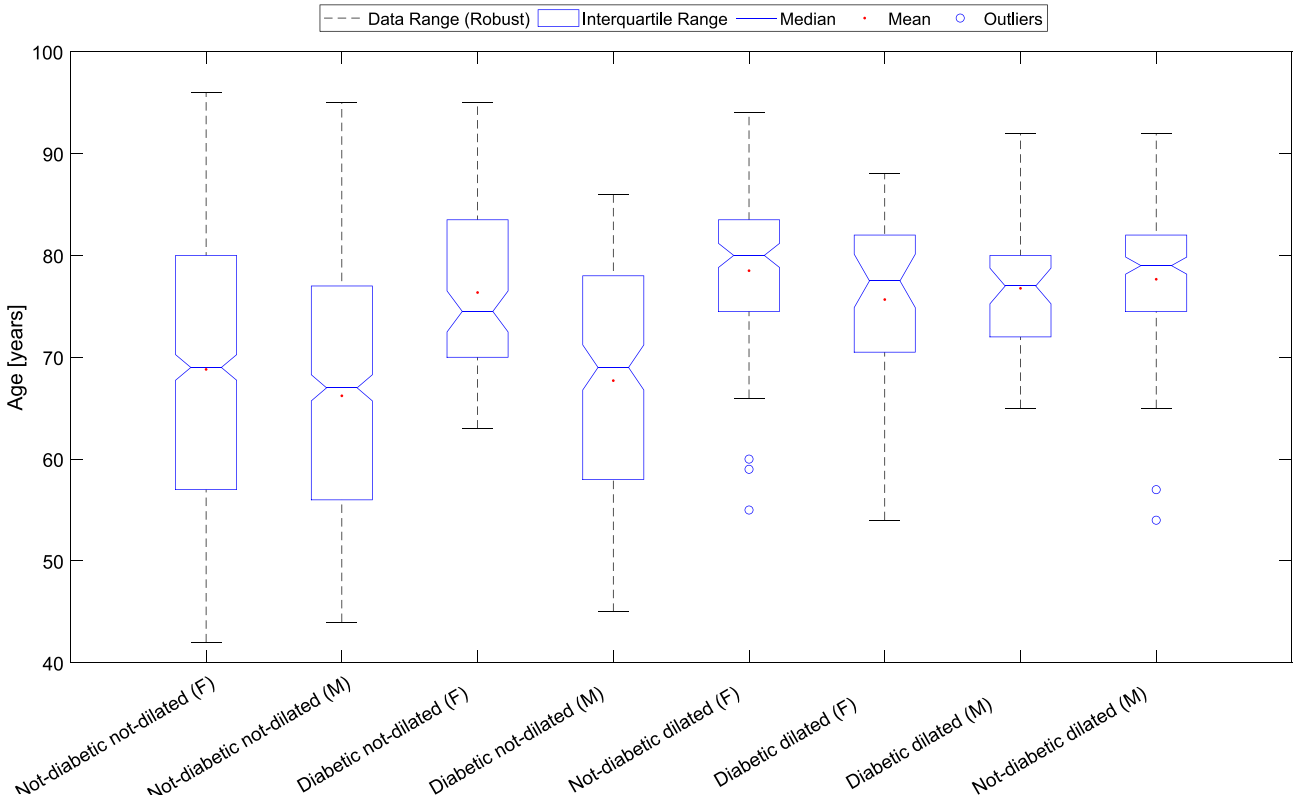

Fig. 3. Mean, median, interquartile ranges and outliers of age values in diabetic and not-diabetic participants having or not dilated cerebral ventricles: gender analysis. Please note that the age difference between dilated and not-dilated scans is about 10 years in diabetic men, whereas it zero in diabetic women.

association found between laboratory and imaging measures in the present cohort suggests that diabetic patients have dilated ventricles more frequently than the general population (24 % vs. 19 %). The borderline significance level of the association is probably attributable to the composition of the cohort examined, which unlike studies in patients with iNPH, also includes neurologically asymptomatic subjects.

Due to the experimental design, anamnestic, clinical, and physiological data corresponding to the scans were unavailable, therefore among scans with Evans index > 0.3 it cannot be quantified how many belong to patients with iNPH and how many to asymptomatic individuals. Please also note that in the absence of clinical data no subject can satisfy the diagnosis even of possible iNPH [16].

In this study, we aimed to distinguish "not-dilated" from "ventricular-enlarged" individuals, with no further interest to whether the latter were iNPH patients. Due to the retrospective design of the study, we had very limited clinical data on the subjects undergoing CT scan, and this scarcity of information prevented us from finding out whether dilated individuals also showed signs or symptoms of the Hakim's triad. This apparent limitation mitigates the weakness of the borderline significance of more prevalent ventricular enlargement in diabetic patients than not-diabetic individuals owing to the inhomogeneity of the dilated group. At the same time, the concurrent contribution of asymptomatic dilated subjects and iNPH patients to the increased frequency detected, advises the clinician (i.e., the diabetologist) to monitor the dilated diabetic patients for the early recognition of possible iNPH neurological symptoms and eventual indication of surgical treatment.

Regardless of full statistical significance, the rate of ventricular enlargement in diabetic patients found in this cohort of scans is of relevance since previous studies reported prevalence data based on indirect measures of the ventricular size. In a large radiological study aimed to describe possible brain lesions, the ventricle-to-brain ratio was found higher in diabetic patients than in not-diabetic individuals [17]. Since then, other heterogeneous measures have been used to quantify tissue alterations in the brain of diabetic patients, and "brain atrophy" or "ventricular enlargement" have been defined "unspecific changes" [18,19].

One reason explaining the more prevalent ventricular enlargement found in diabetic patients than not-diabetic individuals is the influence that diabetes exerts on the glymphatic system, known to be implicated in the pathophysiology of ventricular enlargement [20]. In diabetic rats, MRI scans showed that the clearance of the cerebrospinal fluid contrast agent Gd-DTPA from the interstitial space is slowed by a factor of three in the hippocampus and hypothalamus [21]. Not only this observation gives clues on the relationship between ventricular size and diabetes, but also it helps understand the mechanisms of diabetes-induced cognitive deficits [22].

Analysis of ventricular size, diabetes, sex, and age in the cohort studied here discloses some interesting findings. First is that diabetic patients enlarge their brain ventricles faster (and likely earlier) than not-diabetic individuals. This observation suggests that diabetes promotes mechanisms of ventricular enlargement, possibly by altering the glymphatic system [23]. Women prevail among not-diabetic not-dilated individuals, whereas male prevail among diabetic not-dilated individuals, suggesting that whatever the role played by the female sex in preventing ventricular enlargement, it is lost in the case of diabetes.

Shorter time interval between the mean age of normal and pathological EI values (i.e., "*faster ventricle dilatation*") in diabetic patients is driven predominantly by women, who maintain normal-sized brain ventricles longer than men (approximately 8 years). However, when women's brain ventricles begin to enlarge, they enlarge much faster than in men. Therefore, at least in women, diabetes, sex, and age interact in determining how the brain ventricle size changes with time and in making diabetic women more vulnerable to ventricular enlargement compared to non-diabetic individuals. This is not surprising since sex influences clinical conditions thought linked to glymphatic dysfunction, such as cardiovascular disease [24], Alzheimer's disease [25], Parkinson's disease [26], and recovery from traumatic brain injury [27].

Sex differences in age-dependent loss of cognitive function, proteinopathies, and cardiovascular diseases contrasts with the similar glymphatic fluid transport found in animals of distinct sexes [28,29], notwithstanding young female mice produce 30 % more cerebrospinal fluid than age-matched males [28]. Therefore, underlying differences in genetic susceptibility, and lifestyle resilience between men and women cannot be excluded as contributing factors to the sex differences we observed in our cohort.

In the last years we have investigated the glycaemic measures in some diabetic patients undergoing tap test for probable or possible iNPH (unpublished observations). In these patients, altered blood glucose control and antidiabetic therapy dated back at least a decade. Despite no post-operative change in diet or antidiabetic therapy, some of these patients who underwent shunt for iNPH improved blood glucose control (up to normal levels) and reduced markedly the antidiabetic therapy. On the other hand, not-shunted diabetic patients with iNPH are reported to undergo recurrent episodes of severe hypoglycaemia [30], suggesting that comorbid iNPH-diabetes patients may increase glucose request from brain tissue thereby causing secondary hypoglycaemia [31]. According to this view, diabetes might be interpreted as a compensatory event, secondary to brain glucose deprivation in some brain areas.

The main limitations of the present study are the observational retrospective nature of the design, the relatively small number of patients, the lack of complete clinical data that may introduce a selection bias, the borderline statistical significance. However, the study design and analysis were planned to minimize some of these limitations: the investigation is based on images not on patients, and it is aimed to explore concomitance between neuroimages with abnormal EI values and blood glucose measures with "diabetic" plasma concentrations. Categorization into diabetic patients and non-diabetic individuals "with the 1-hour glycemia criterion" has reduced the sample size with an indirect effect on the statistical significance of multivariate logistic regression. Consequently, in the series of patients analysed, the influence of diabetes on ventricular enlargement did not statistically resist the confounding effect of age and gender. It is reasonable to assume that since the effect of diabetes is weaker than that of age and sex, the size of the sample on which the multivariate analysis was carried out was not such as to guarantee its full expression. This makes it mandatory to address the issue by studying diabetic patients recruited from a tertiary center and verifying how many of them have ventricular enlargement compared to age- and sex-matched normoglycaemic individuals. Such an investigation has been designed, data collection has been concluded, and data analysis is in progress.

5. Conclusions

Our preliminary study confirms an association between ventricular enlargement and diabetes. **Diabetic** patients have a high prevalence of ventricular dilatation and a short time interval between the mean age for non-dilated and dilated patients, especially diabetic women. Both sex and age interact in enlarging brain ventricles in both **not-diabetic** individuals and **diabetic** patients, but a conservative interpretation of the present data suggests that after the age of 70 years diabetes may concur too, especially in women. A routine brain imaging examination may be therefore advisable in these **diabetic** patients, yet centrally neurologically asymptomatic, to foresee abnormal ventricular enlargement and possible neurological symptoms of iNPH. A further study from a tertiary diabetic centre is nearing completion to validate the prevalence of pathological ventricular enlargement, in diabetic patients and their comorbidities.

Author contributions

AC, PG, FF, PM: contributing to conception and design, analyzing and interpreting data, drafting the manuscript, approving the final content of the manuscript. RG, SP, CT, LP, LM, NLB, AC, RG, PG, FF, PM: analyzing and interpreting data, drafting and revising the manuscript, approving the final content of the manuscript. AR, SP, PM: acquiring and interpreting data, drafting and revising the manuscript, approving the final content of the manuscript.

Ethical statement

The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Antonio Currà: Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Data curation. **Riccardo Gasbarrone:** Software, Formal analysis. **Patrizia Gargiulo:** Formal analysis, Data curation. **Aurelia Rughetti:** Investigation, Data curation. **Simone Peschillo:** Validation, Supervision. **Carlo Trompetto:** Validation, Supervision, Formal analysis. **Luca Puce:** Validation, Supervision, Investigation. **Lucio Marinelli:** Validation, Supervision. **Francesco Fattapposta:** Validation, Supervision, Formal analysis. **Nicola Luigi Bragazzi:** Validation, Supervision. **Paolo Missori:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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