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Original Research Article

Role of Multi-Parametric MRI in Assessing Brain Changes in Diabetes Mellitus: from Diagnosis to Therapy

Kishan Kumar Thakur[1], Mithilesh Pratap[2], Pranav Kumar Santhalia[3]

[1]Senior Resident, Department of Radiology, Nalanda Medical College Hospital, Patna, Bihar
[2]Professor, Department of Radiology, Nalanda Medical College Hospital, Patna, Bihar
[3]Assistant Professor, Department of Radiology, Nalanda Medical College Hospital, Patna, Bihar

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Corresponding Author: Dr. Mithilesh Pratap
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Abstract:

Background: While entities like "diabetic foot," "diabetic eye," and "diabetic kidney" are well-known, the concept of a "diabetic brain" remains less explored. Brain involvement in diabetes is established, but understanding the precise effects of glycemic variations on the brain at different levels—macroscopic to molecular—is still under scrutiny. This study used multifunctional and morphological MRI to evaluate these effects and proposed clinical variables for routine assessment of diabetic brain changes.

Aims and Objectives: To meta-analyze evidence supporting and refuting the concept of the 'Diabetic Brain' using regional population-based imaging experiences. Primary objective: Evaluate the role of Multi-parametric MRI in diabetes at diagnosis and during therapy. Secondary objective: Illustrate longitudinal changes in newly diagnosed and established diabetes using Multi-parametric MRI.

Materials and Methods: This diagnostic study was conducted in the Department of Radiology at Nalanda Medical College Hospital, Patna, Bihar from September 2022 to August 2023. It included 125 patients selected using purposive sampling from those admitted to Nalanda Medical College Hospital with clinically diagnosed diabetes mellitus with an indication of MRI.

Results: Morphological Imaging Features:- Includes ischemic foci like large territorial and small lacunar infarcts, chronic white matter changes from small vessel disease, microbleeds, signs of normal pressure hydrocephalus, generalized and regional brain atrophy, and small vessel stenosis on MR angiography. Functional Imaging Features:- Arterial spin labeling shows reduced global perfusion. MR spectroscopy indicates decreased N-acetyl aspartate and increased myo-inositol, with decreased total creatine and choline, and elevated glutamine-glutamate complex. Diffusion-weighted imaging reveals globally increased apparent diffusion coefficient (ADC), especially in the periventricular region. Diffusion tensor imaging shows reduced fractional anisotropy (FA) and increased mean diffusivity (MD), with elevated radial diffusivity (RD) and decreased axial diffusivity (AD) compared to controls.

Discussion: The integrated findings from morphological and functional imaging highlight the intricate interplay between vascular, structural, and metabolic changes in diabetic brains. These imaging modalities collectively provide a comprehensive assessment of neurovascular pathology in diabetes, offering insights into disease progression and potential therapeutic targets.

Conclusion: The diabetic brain undergoes changes early in the disease process, preceding other organ complications associated with diabetes. However, due to the brain's remarkable ability to redistribute functions to healthy areas when primary areas are affected, these pathological processes often remain hidden until advanced stages. MRI remains indispensable and the gold standard for detecting and quantifying brain changes in type 2 diabetes patients.

Introduction

Diabetic foot, nephropathy, neuropathy, amyotrophy, and retinopathy have been extensively studied in medical literature since the inception of knowledge about this condition. Additionally, diabetic vasculopathy has gained recognition for its direct or indirect role in various end-organ complications, including those affecting the human brain. This study aims to investigate whether diabetes, often termed the "emperor of all maladies," also affects brain cells, potentially giving rise to a concept known as the "Diabetic Brain." [1] This exploration is inspired by the CASCADE consortium's findings suggesting ongoing brain pathology directly linked to diabetes rather than secondary effects like atherosclerosis or hypertension [2] Magnetic resonance imaging

(MRI) remains the gold standard for assessing these brain changes, offering detailed anatomical and functional insights crucial for understanding diabetes-related brain pathology. [3] The underlying mechanisms and impact of both acute and chronic fluctuations in blood sugar levels on the human brain remain inadequately understood and are currently under scrutiny. The study will conduct a comprehensive analysis of current evidence regarding type 2 diabetes's impact on the human brain using MRI, drawing from our experience at a large hospital where diabetes is prevalent among our patient population.

Aims and Objectives

To meta-analyse evidence supporting and refuting the concept of the 'Diabetic Brain' using regional population-based imaging experiences. Primary objective: Evaluate the role of Multi-parametric MRI in diabetes at diagnosis and during therapy. Secondary objective: Illustrate longitudinal changes in newly diagnosed and established diabetes using Multi-parametric MRI.

Materials and Methods

This diagnostic study was conducted in the Department of Radiology at Nalanda Medical College Hospital, Patna, Bihar from September 2022 to August 2023. It included 12t patients selected using purposive sampling from those admitted to Nalanda Medical College Hospital with clinically diagnosed diabetes mellitus with an indication of MRI. Patients underwent MRI Brain on 1.5 Tesla with 8-channel bird cage coil with following sequences.

- T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) sequences

-Three-dimensional T1-weighted sequence (MPRAGE)

- Three-dimensional time of flight (TOF) angiogram

- Multivoxel magnetic resonance spectroscopy (MRS)

- Arterial spin labeling (2D-PASL)

- Diffusion tensor imaging (DTI)

Cases:

Inclusion Criteria: Patients diagnosed with diabetes mellitus were included if they required an MRI that did not interfere with diabetes-related brain pathology. Hypertension was considered due to its intertwined relationship with diabetes, making separation challenging.

Exclusion Criteria: Patients with co-existing conditions such as cardiac disease, endocrinopathies, metabolic disorders, genetic disorders, history of cardiac arrest or seizures, CNS infections, trauma, or malignancies were excluded. Those diagnosed with dementia were also not included.

Controls:

- Age-matched controls were selected from patients presenting with unrelated disorders.

- Individuals with dementia were specifically excluded from the control group.

Results

In a prospective evaluation, approximately 125 MRI brain scans were conducted on known diabetic patients at the MRI unit of the Department of Radiology, Nalanda Medical College and Hospital, Patna, Bihar. These patients had documented diabetes mellitus ranging from recent diagnoses to many years. The study did not aim to correlate clinical details with imaging features beyond confirming type 2 diabetes. All patients were under routine medical follow-up, and MRI scans were performed for unrelated medical reasons, primarily for suspected neurovascular issues.

Of the initial scans, 45 were excluded due to complicating factors or MRI artifacts. This left 85 scans for analysis, comprising 57 males and 28 females. Age-matched controls (n=34) without a history of diabetes were also included for comparison.

Clinical Observation: Cognitive impairment was noted in a majority of patients.

Morphological Imaging Features: Includes ischemic foci like large territorial and small lacunar infarcts, chronic white matter changes from small vessel disease, microbleeds, signs of normal pressure hydrocephalus, generalized and regional brain atrophy, and small vessel stenosis on MR angiography.

Functional Imaging Features:- Arterial spin labeling shows reduced global perfusion. MR spectroscopy indicates decreased N-acetyl aspartate and increased myo-inositol, with decreased total creatine and choline, and elevated glutamine-glutamate complex. Diffusion-weighted imaging reveals globally increased apparent diffusion coefficient (ADC), especially in the periventricular region. Diffusion tensor imaging shows reduced fractional anisotropy (FA) and increased mean diffusivity (MD), with elevated radial diffusivity (RD) and decreased axial diffusivity (AD) compared to controls.

Discussion

Diabetes mellitus is recognized more for its impact on morbidity rather than mortality. Chronic hyperglycemia is primarily responsible for the end-organ changes that lead to dysfunction in affected organs. [4] In studies involving diabetic patients,

including ours, there is often a higher proportion of males compared to other genders. [5] In our study, none of the patients exhibited symptoms of transient ischemia or major cerebrovascular accidents, which were excluded as confounding factors.

White matter changes, visible as focal or diffuse hyperintensities on T2-weighted and FLAIR images, are consistently noted in diabetic patients across various studies, including ours. Brain atrophy, particularly in areas with dense white matter tracts like the forceps major, correlates well with fractional anisotropy values. Although lacunar infarcts were observed in our study, neither our findings nor those of other studies have conclusively differentiated their role from neuronal loss in causing brain atrophy. [6]

Some studies have explored differential brain atrophy patterns across different brain regions and their correlation with altered brain function. [7] While our assessment did not yield significant results in certain areas such as the hippocampi, brain stem, and cerebellum, there was a trend towards significance in the differences between cases and controls, which might be refined with larger sample sizes.

Although our study did not delve into 3D volumetric assessments, we did observe correlations between white matter loss on DTI parameters and atrophy, particularly in areas like the forceps major and centrum semiovale of the frontal and parietal lobes. Significant differences between cases and controls were observed in ADC values and the first eigen vector.

Furthermore, our study highlighted significant inter-correlations among DTI parameters in various white matter regions, indicating a neurodegenerative process characterized by decreased N-acetylaspartate (NAA), reduced fractional anisotropy, and altered first eigen vector values. Elevated trace values and ADC further confirmed neuronal or white matter tract loss, possibly due to reparative processes involving increased glial tissue. [8]

While several large studies have established the association of diabetes with brain atrophy, none have comprehensively evaluated the specific white matter changes depicted by functional MRI in relation to brain atrophy. [9] Microvascular changes in the brain and macrovascular changes in both the brain and extracranial carotid arteries, often due to atherosclerosis and hypertension, play a pivotal role in initiating subsequent pathological changes. [10] These alterations result in a complex interplay of chronic low-grade ischemia and reperfusion bleeds, which ultimately lead to structural changes in neuronal tissue and the broader brain parenchyma. [11]

Studies have consistently demonstrated that reduced and altered cerebral blood flow (CBF) in diabetic individuals correlates with white matter changes, a relationship that significantly differs from non-diabetic controls. [12] Furthermore, research has suggested a modest association between diabetes and the occurrence of intracranial bleeds, impacting outcomes in affected individuals. [13]

There is also a proposed link between beta-amyloid deposition and oxidative stress induced by altered energy metabolism in both diabetes and conditions like Alzheimer's disease and dementia. [14] This connection underscores potential shared mechanisms contributing to neurodegenerative processes in these diseases. [15]

These findings highlight the multifaceted impact of diabetes on brain health, involving vascular changes, cerebral blood flow alterations, and potential interactions with neurodegenerative pathways, thereby emphasizing the need for further investigation into their complex interrelationships.

The integrated findings from morphological and functional imaging highlight the intricate interplay between vascular, structural, and metabolic changes in diabetic brains. These imaging modalities collectively provide a comprehensive assessment of neurovascular pathology in diabetes, offering insights into disease progression and potential therapeutic targets. The observed ischemic foci, white matter changes, and microvascular alterations underscore the significant cerebrovascular burden associated with diabetes, potentially contributing to cognitive decline and other neurological complications. Understanding these imaging biomarkers is crucial for early detection, monitoring disease progression, and evaluating treatment efficacy in diabetic patients. Future research should focus on longitudinal studies to elucidate temporal relationships between these imaging markers and clinical outcomes, aiming to improve management strategies and outcomes for individuals with diabetic neurovascular complications.

Conclusion

Based on the data from our study, it would be reasonable to conclude that there is indeed a distinct entity referred to as the "Diabetic Brain," analogous to other well-known diabetic complications such as the diabetic foot, eye, kidney, and neuropathy. The presence of diabetic brain changes precedes the development of other end-organ complications typically associated with diabetes. However, due to the brain's remarkable ability to redistribute functions to healthy areas when primary functions are compromised, these pathological processes often remain hidden until later stages. MRI continues to be the cornerstone modality and the gold standard for detecting and quantifying brain changes in patients with type 2 diabetes.

These points underscore the importance of recognizing and studying the diabetic brain as a unique entity, distinct from other diabetic complications, and highlight the pivotal role of MRI in advancing our understanding of its pathophysiology and clinical implications.

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