ISSN: 2634 - 680X

Journal of Clinical Case Studies Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Diabetes and Neurologic Diseases in a Developing Country

Castejón OJ[1]*, Carrero Gonzalez CM[2], Lastre G[2], Galindez P[3], Leal J[1], Salones de Castejón M[3] and Sierra Carrero L[4]

[1]Instituto de Investigaciones Biológicas "Drs. Orlando Castejón and Haydee Viloria de Castejón", Venezuela

[2]Facultad de Ciencias de la Salud. Universidad Simon Bolivar. Barranquilla, Colombia

[3]Instituto de Neurociencias Clínicas, Fundación Castejón, Hogar Clínica San Rafael. Maracaibo, Venezuela

[4]Programa de Medicina, Universidad del Norte, Barranquilla, Colombia

SUMMARY

In the present clinical and observational study we have analyzed sixteen patients with type II diabetes, ranging from 56 to 88 years-old., and showing blood hypertension (84%) %), cardiovascular diseases (43%), memory disorder (43%), Parkinson disease (31%), Headaches (25%),. Sleep disorders (18%), gait disturbances (18%), language disorders (18%), dizziness and vertigo (12%), cervicogenic headache (12%) liver diseases (12%), gastrointestinal disease (12%) arthritis (12%), respiratory diseases (6%), Alzheimer disease (6%), and previous cerebrovascular accident (6%). We have diagnosed six mixed syndromes of diabetes and Parkinson disease (37%), three patients with diabetes and Alzheimer disease (18%) two cases with diabetes, blood hypertension and Alzheimer disease (12%) and two case with diabetes and cervicogenic headaches (12%). The pathophysiological mechanisms involved are described in each case. A relationship of diabetic patient lifestyle with environmental conditions, low socioeconomic status and family history is postulated.

***Corresponding author**

Castejón OJ, Instituto de Investigaciones Biológicas "Drs. Orlando Castejón and Haydee Viloria de Castejón", Venezuela. E-mail: ocastejo@gmail.com

Received: June 12, 2020; **Accepted:** July 15, 2020; **Published:** August 22, 2020

Keywords: Diabetes type II, Blood hypertension, Cardiovascular disease, Parkinson disease, Aging patients, Neurological disease, Metabolic diseases.

Introduction

Diabetes Cognitive dysfunction and dementia

Patients with diabetes have an increased risk of developing cognitive impairment in comparison with the general population. Cognitive dysfunction comprises impairments of executive functions, memory, attention, and psychomotor efficiency. The main risk factors for cognitive impairment in diabetes are considered to be chronological age, duration of diabetes, and coexistent microvascular and macrovascular complications [1,2].

In addition to age-related cognitive decline there is a higher risk of going on to develop vascular dementia and Alzheimer's disease associated with aspects of modern lifestyle. Epidemiological evidence suggests an increased risk of developing dementia (including Alzheimer's disease) in individuals with obesity and type 2 diabetes but also in those with poor insulin sensitivity without diabetes, implicating a mechanistic link between adiposity, insulin sensitivity and dementia. Insulin receptors are expressed in the brain and physiological roles for insulin in the CNS are starting to be delineated. Indeed disrupted neuronal insulin action may underlie the link between diabetes and neurodegenerative disorders [3].

Cumulative epidemiological evidence suggested that vascular and vascular-related factors may be important for the development of age-related cognitive decline, mild cognitive impairment, and cognitive decline of degenerative (Alzheimer's disease, AD) or vascular origin (vascular dementia, VaD). Among vascular-related factors, metabolic syndrome (MetS) has been associated with the reduced risk of predementia syndromes, overall dementia, and VaD, but contrasting findings also exist on the possible role of MetS in AD [4].

A growing body of epidemiological evidence suggested that metabolic syndrome (MetS) and Mets components (impaired glucose tolerance, abdominal or central obesity, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol) may be important in the development of age-related cognitive decline, mild cognitive impairment, vascular dementia, and Alzheimer's disease (AD). These suggestions proposed in these patients the presence of a "metabolic-cognitive syndrome", i.e. a MetS plus cognitive impairment of degenerative or vascular origin. This could represent a pathophysiological model in which to study in depth the mechanisms linking metabolic syndrome and MetS components with dementia, particularly AD, and predementia syndromes, suggesting a possible integrating view of the MetS components and their influence on cognitive decline [5].

Previous epidemiologic studies indicate that diabetes mellitus is associated an increased risk of developing Alzheimer disease in people who do not have dementia [6]. Epidemiological and biological evidences support a link between type 2 diabetes mellitus and Alzheimer's disease. Cognitive deficits in persons with diabetes mainly affect the areas of psychomotor efficiency, attention, learning and memory, mental flexibility and speed, and executive function. The strong epidemiological association has suggested the existence of a physiopathological link. Hyperglycemia itself is a risk factor for cognitive dysfunction and dementia. Hypoglycemia may also have deleterious effects on cognitive function [7].

Methods

We have clinical study sixteen patients ranging from 56 to 88 years-old. They were studied at the Neuroscience Outpatient Clinic of Clinical Neuroscience Institute at San Rafael Clinical Home in Maracaibo. Venezuela. In some patients nuclear magnetic resonance images were correlated with clinical data. This study was carried out following the ethical principles of Helsinki Declaration for Research in Human Beings and approved by the Ethical Committee of Biological Research Institute. A consent was obtained from the patients and/ or family patient.

Results

Case Report

Case 1: MN, Type II diabetes, 56 years old, F. Intense headache and neck pain. High blood pressure, Fat liver, Gall lithiasis and colecystitis. NMR images showed curvature of cervical spine, osteophytes and osteoporosis.

Case 2: CB, 81 years old, F. Type II diabetes, Blood hypertension. Obesity. Intense headache irradiated to neck and dorsal spine. Cervical osteophytes and osteoporosis, gallstones and cholecystitis

Case 3: AA, 64 years old, M. Diabetes type II and Parkinson Disease characterized by resting tremor in left hand, bradykinesia, decreased force in both legs, and sleep disorders.

Case 4: JA, 76 years old, M. diabetes type II and Parkinson disease features by tremor in both hands, arterial hypertension, severe coronary obstructive diseases and open cardiac surgery, and ptosis palpebral.

Case 5: JL, 84 years old, M. Diabetes type II and Parkinson disease exhibiting tremor in right hand since three years ago, arterial hypertension, arthritis, disorders of language and memory,

Case 6: LZ, 76 years-old, F. Diabetes type II and Parkinson disease with tremor in right hand and arm, bradykinesia, rigidity, arterial hypertension, bradycardia, previous ischemic cerebrovascular accident and sleep disorder, respiratory obstructive disease. Father and mother with family history of Parkinson disease.

Case 7: JR, 84 years-old, M. Diabetes type II, Parkinson disease and Alzheimer disease characterized by right hand tremor and language disorders Semantic and working memory disorders. Patient in a wheel chair by generalized arthritis, and loss of sphincter control.

Case 8: JL, 84 years old, M. Diabetes type II and Parkinson disease characterized by tremor in right hand since three years ago and disorders of languages, blood hypertension, arthritis, and semantic memory disorders.

Case 9: MF. 58 years old, F. Diabetes type II. Severe blood hypertension, Patients with six ischemic strokes in the last ten years, Woman with smoking habit during 40 years, insomnia, blurred vision, gait disturbances. RMN images showed cerebral atrophy, deep cortical sulcus, hypodense lesion in left parieto-occipital region, ventriculomegaly, scarce differentiation between white matter and gray matter.

Case 10: JC, 66 years old, F. Diabetes type II. Blood hypertension, Hemorrhagic stroke and right hemiparesis, cardiac failure. NMR image showed left fronto-temporal hemorragic infarction.

Case 11: OU, 56 years old, M. Diabetes type II. Blood hypertension. Patient suffered ischemic cerebrovascular accident one year ago. Gait disturbances, and loss of memory. Crambs in right hemifacial region, legs, feet and arms. NMR images showed irritable vowel syndrome. Eco Doppler showed segmentary stenosis of carotid system.

Case 12: CN, 70 years old, M. Diabetes type II and arterial hypertension since 10 years ago. Patient suffered ischemic cerebrovascular accident 15 days ago, showing vertigo, temporo-spacial disorientation. NMR images showed stenotic vascular changes of Willis Circle, vertebral and cerebral arteries

Case 13: JP, 75 years-old, F. Diabetes type II. Blood hypertension. Loss of semantic memory, dizziness, vertigo, frontal-temporal-occipital headache, loss of body weight, and sleep disorders.

Case 14: LG. 81 years old, F. Diabetes type II. Blood hypertension, Alzheimer disease, Loss of semantic and working memory, insomnia, holocraneal cephalea, Family history of Alzheimer disease.

Case 15: LR, 64 years-old, F. Diabetes type II and Alzheimer Disease. Episodic and working memory disorders, gait disturbances, blood hypertension, hypothyroidism and hearth failure

Case 16: JP, 65 years-old, F. Diabetes type II, blood hypertension, tremor, Episodic memory disorders, frontal-parietal-occipital pulsatile headache, dizziness, diminution of visual acuity and sleep disorders.

Interpretation of Results

In the present clinical and observational study we have analyzed sixteen patients with Type II diabetes (100%), blood hypertension (84%) %), cardiovascular diseases (43%), memory disorder (43%), Parkinson disease (31%), Headaches (25%), sleep disorders (18%), gait disturbances (18%), dizziness and vertigo (12%) liver diseases (12%), gastrointestinal disease (12%) arthritis (12%), language disorders (18%), respiratory diseases (6%), Alzheimer disease (6%), cervicogenic headache with headache and neck pain (12%) and previous cerebrovascular accident (6%).

Discussion

Diabetes and memory disorders

We have found memory disorder (43%) in the diabetic patients examined. A primary distinguishing feature of type 2 diabetes is that people with this disorder often (but not invariably) do poorly on measures of learning and memory, whereas deficits in these domains are rarely seen in people with type 1 diabetes. Chronic hyperglycaemia and microvascular disease contribute to cognitive dysfunction in both type 1 and type 2 diabetes, and both disorders are associated with mental and motor slowing and decrements of similar magnitude on measures of attention and executive functioning. Additionally, both types are characterized by neural slowing, increased cortical atrophy, microstructural abnormalities in white matter tracts, and similar, but not identical, changes in concentrations of brain neurometabolites [8].

Diabetes and Parkinson disease

We have diagnosed six mixed syndromes of diabetes and Parkinson disease (37%). Parkinson disease (PD) is a progressive neurodegenerative disorder affecting motor and cognitive functions. Prior studies showed that patients with PD and diabetes (DM) demonstrate worse clinical outcomes compared to non-diabetic subjects with PD. DM may exacerbate brain atrophy and cognitive functions in PD with greater vulnerability in the frontal lobes. Given the high prevalence of DM in the elderly, delineating its effects on patient outcomes in the PD population is of importance [9].

According to Bohnen et al. (2014), diabetes mellitus is independently associated with more severe cognitive impairment in PD likely through mechanisms other than disease-specific neurodegenerations [10]. Diabetes mellitus may predispose toward a Parkinson-like pathology, and when present in patients with Parkinson disease, can induce a more aggressive phenotype [11].

While many oxidative stress and reactive oxygen species (ROS) are intracellular signaling messengers and most products of oxidative metabolisms are beneficial for normal cellular function, the elevation of ROS levels by light, hyperglycemia, peroxisomes, and certain enzymes causes oxidative stress-sensitive signaling, toxicity, oncogenesis, neurodegenerative diseases, and diabetes. Although the underlying mechanisms of these diseases are manifold, oxidative stress caused by ROS is a major contributing factor in their onset [12].

De Pablo-Fernandez et al. (2018) reported an increased rate of subsequent PD following T2DM in a large cohort study. Their findings may reflect shared genetic predisposition and/or disrupted shared pathogenic pathways with potential clinical and therapeutic implications [13].

Diabetes and headaches

We have herein reported headaches (25%) in the patients under study. Two patients showed cervicogenic headaches with typical NMR images of cervical spine pathology. Another patient showed pulsatile headache and blood hypertension, and other patient with headache and Alzheimer disease. In patients with diabetes mellitus (DM), there are changes in vascular reactivity and nerve conduction that may be relevant for headache and migraine pathophysiology. However, previous studies on the relationship between headache and DM have shown conflicting results [14]. Other Authors reported no clear association between headache and type 2 DM [15].

Diabetes and Alzheimer disease

In the present study we have diagnosed three patients with diabetes and Alzheimer disease (18%), two patients coexisting with blood hypertension, and one case with Parkinson disease. The incidence of Alzheimer disease (AD) and diabetes mellitus (DM) is increasing at an alarming rate and has become a major public health concern worldwide. Recent epidemiological studies have provided direct evidence that DM is a strong risk factor for AD; this finding is now attracting attention. However, the underlying mechanisms for this association remain largely unknown. Previous in vitro and in vivo studies reported that diabetic conditions could cause an increase in the beta-amyloid peptide (Aβ) levels, which exhibits neurotoxic properties and plays a causative role in AD. It has been shown that insulin signaling is involved in a variety of neuronal functions, and that it also plays a significant role in the pathophysiology of AD. Thus, the modification of neuronal insulin signaling by diabetic conditions may contribute to AD progression. Another possible mechanism is cerebrovascular alteration, a common pathological change observed in both diseases. Accumulating evidence has suggested the importance of Aβ-induced cerebrovascular dysfunction in AD, and indicated that pathological interactions between the receptor for advanced glycation end products (RAGE) and Aβ peptides may play a role in this dysfunction [16].

Accumulating evidence has suggested the importance of Aβ-induced cerebrovascular dysfunction in AD, and indicated that pathological interactions between the receptor for advanced glycation end products (RAGE) and Aβ peptides may play a role in this dysfunction. Emerging insights into the mechanistic link between neuronal receptors and soluble Aβ oligomers highlight the potential role of these receptors in Aβ-mediated neurotoxicity in AD. Additionally, neuronal receptors such as insulin, amylin and receptor for advanced glycation end products could be potential targets for soluble Aβ-oligomer-mediated neurotoxicity. Aβ interactions with other receptors such as the p75 neurotrophin receptors, which are highly expressed on cholinergic basal forebrain neurons lost in AD, are also highlighted [17].

Previous studies have shown that Aβ binds to nicotinic acetylcholine receptors (nAChRs) and activates signaling cascades that result in the disruption of synaptic functions. These findings suggest a possible link between impaired cholinergic neurotransmitter function in AD and Aβ pathogenesis [18].

Alzheimer's disease (AD) is associated with a perturbation in different membrane properties. Amyloid-β (Aβ) plaques and neurofibrillary tangles of tau protein together with neuroinflammation and neurodegeneration are the most characteristic cellular changes observed in this disease. The extracellular presence of Aβ peptides forming senile plaques, together with soluble oligomeric species of Aβ, are considered the major cause of the synaptic dysfunction of AD. It has been postulated that Chol content and Chol distribution condition Aβ production and posterior accumulation in membranes and, hence, cell dysfunction. Several lines of evidence suggest that Aβ partitions in the cell membrane accumulate mostly in raft domains, the site where the cleavage of the precursor AβPP by β- and γ- secretase is also thought to occur. The main consequence of the pathogenesis of AD is the disruption of the cholinergic pathways in the cerebral cortex and in the basal forebrain. In parallel, the nicotinic acetylcholine receptor has been extensively linked to membrane properties. Since its trans membrane domain exhibits extensive contacts with the surrounding lipids, the acetylcholine receptor function is conditioned by its lipid microenvironment. The nicotinic acetylcholine receptor is present in high-density clusters in the cell membrane where it localizes mainly in lipid-ordered domains. Perturbations of sphingomyelin or cholesterol composition alter acetylcholine receptor location. Therefore, Aβ processing, Aβ partitioning, and acetylcholine receptor location and function can be manipulated by changes in membrane lipid biophysics [19].

Recent studies using the human brain indicate that insulin signaling is impaired in the AD brain. In neurons, this insulin signaling plays a key role in modulating synaptic function and neuronal senescence besides regulating tau phosphorylation, another hallmark of AD. On the other hand, in cerebral vessels, DM causes vascular remodeling, which involves increased RAGE (receptor for advanced glycation endproducts) expression, and AD is associated with cerebrovascular amyloid angiopathy (CAA). Moreover, insulin signaling is also involved in the mechanism of aging, decreasing with an increase in age [20].

Chronic hyperglycemia and hyperinsulinemia primarily stimulates the formation of Advanced Glucose Endproducts (AGEs), which leads to an overproduction of Reactive Oxygen Species (ROS). Protein glycation and increased oxidative stress are the two main mechanisms involved in biological aging, both being also probably related to the etiopathogeny of AD. Besides its traditional glucoregulatory importance, insulin has significant neurothrophic properties in the brain. How can clinical hyperinsulinism be a risk factor for AD whereas lab experiments evidence insulin to be an important neurothrophic factor? These two apparent paradoxal findings may be reconciliated by evoking the concept of insulin resistance. Whereas insulin is clearly neurothrophic at moderate concentrations, too much insulin in the brain may be associated with reduced amyloid-beta (Abeta) clearance due to competition for their common and main depurative mechanism - the Insulin-Degrading Enzyme (IDE). Since IDE is much more selective for insulin than for Abeta, brain hyperinsulinism may deprive Abeta of its main clearance mechanism. Hyperglycemia and hyperinsulinemia seems to accelerate brain aging also by inducing tau hyperphosphorylation and amyloid oligomerization, as well as by leading to widespread brain microangiopathy. In fact, diabetes subjects are more prone to develop extense and earlier-than-usual leukoaraiosis (White Matter High-Intensity Lesions - WMHL). WMHL are usually present at different degrees in brain scans of elderly people. People with more advanced WMHL are at increased risk for executive dysfunction, cognitive impairment and dementia. Clinical phenotypes associated with insulin resistance possibly represent true clinical models for brain and systemic aging [21].

Diabetes, Blood hypertension and Alzheimer disease

We have above described two cases of diabetes, blood hypertension and Alzheimer disease (12%) and one case with diabetes, Parkinson disease and Alzheimer disease (6%). Therefore, elucidating the molecular interactions between diabetes and AD is of critical significance because it might offer a novel approach to identifying mechanisms that may modulate the onset and progression of sporadic AD cases [22]. In addition, according to our study it is interesting to study the molecular interactions among diabetes, AD and PD..

An increasing number of studies have demonstrated a connection between Alzheimer's disease (AD) and diabetes, particularly type 2 diabetes (T2D). The risk for developing T2D and AD increases exponentially with age and having T2D increases the risk of developing AD. The involvement of mitochondrial abnormalities and oxidative stress in AD and diabetes highlight the similarities between both pathologies [23]. The fact that mitochondria are the major generators and direct targets of reactive oxygen species led several investigators to foster the idea that oxidative stress and damage in mitochondria are contributory factors to several disorders including Alzheimer's disease and diabetes. Since brain possesses high energetic requirements, any decline in brain mitochondria electron chain could have a severe impact on brain function and particularly on the etiology of neurodegenerative diseases [24,25].

The pathomechanism of Alzheimer's disease (AD) certainly involves mitochondrial disturbances, glutamate excitotoxicity, and neuroinflammation. The three main aspects of mitochondrial dysfunction in AD, i.e., the defects in dynamics, altered bioenergetics, and the deficient transport, act synergistically. In addition, glutamatergic neurotransmission is affected in several ways. The balance between synaptic and extrasynaptic glutamatergic transmission is shifted toward the extrasynaptic site contributing to glutamate excitotoxicity, a phenomenon augmented by increased glutamate release and decreased glutamate uptake. Neuroinflammation in AD is predominantly linked to central players of the innate immune system, with central nervous system (CNS)-resident microglia, astroglia, and perivascular macrophages having been implicated at the cellular level. Several abnormalities have been described regarding the activation of certain steps of the kynurenine (KYN) pathway of tryptophan metabolism in AD. First of all, the activation of indolamine 2,3-dioxygenase, the first and rate-limiting step of the pathway, is well-demonstrated. 3-Hydroxy-L-KYN and its metabolite, 3-hydroxy-anthranilic acid have pro-oxidant, antioxidant, and potent immunomodulatory features, giving relevance to their alterations in AD. Another metabolite, quinolinic acid, has been demonstrated to be neurotoxic, promoting glutamate excitotoxicity, reactive oxygen species production, lipid peroxidation, and microglial neuroinflammation, and its abundant presence in AD pathologies has been demonstrated. Finally, the neuroprotective metabolite, kynurenic acid, has been associated with antagonistic effects at glutamate receptors, free radical scavenging, and immunomodulation, giving rise to potential therapeutic implications [26,27].

Dementia is an increasingly prevalent condition that intersects worldwide with the epidemic of type 2 diabetes mellitus (DM2). It would seem logical to expect that the occurrence of DM2 increases the likelihood of developing dementia, due to its deleterious effect on the cerebral vasculature and the associated hormonal and metabolic changes. Many reports indicate that it also increases the risk of developing Alzheimer's disease (AD). Genetically engineered animal models of the condition deteriorate more severely when there is a concomitant insulin resistant brain state (IRBS). Furthermore, IRBS alone is associated with anatomical, behavioral, and molecular changes that justify the proposal that AD may be due to an IRBS. This is explored in the context of accumulating evidence that the IRBS need not be related to peripheral insulin resistance, and that administration of insulin directly to the brain improves selected cognitive parameters targeted in AD. This view is consistent with the Damage Signals hypothesis of AD pathogenesis, which can help unifying the pleiotropic effects of agents toxic to insulin-producing/secreting (e.g., pancreatic β) cells, as well as IRBS caused by different mechanisms in AD [28].

Diabetes and sleep disorders

We have found sleep disorders (18%) in the patients examined. Diabetes and sleep disorders. Any qualitative or quantitative disturbances in sleep would result in an increased prevalence of obesity, metabolic disorders, diabetes, cardiovascular diseases, and hypertension. Different sleep habits can interfere with diabetes, excluding sleep breathing disorders, and successively looks at the effects of sleep duration, chronotype and social jet lag on the risk of developing diabetes as well as on the metabolic control of both type 1 and type 2 diabetes [29].

The relationship between sleep disturbances and diabetes is dual-sided, as chronic sleep disturbances would elevate the risk of developing insulin resistance, while diabetes would worsen the quality of sleep. Both the qualitative and quantitative disturbances in sleep significantly increase the risk of developing diabetes, which is supported by numerous community-based and hospital-based epidemiological studies [30].

Sleep-disordered breathing (SDB) encompasses a spectrum of conditions that can lead to altered sleep homeostasis. In particular, obstructive sleep apnoea (OSA) is the most common form of SDB and is associated with adverse cardiometabolic manifestations including hypertension, metabolic syndrome and type 2 diabetes, ultimately increasing the risk of cardiovascular disease. The pathophysiological basis of these associations may relate to repeated intermittent hypoxia and fragmented sleep episodes that characterize OSA which drive further mechanisms with adverse metabolic and cardiovascular consequences [31].

Diabetes and gait disturbances

We have reported gait disturbances in 18% of diabetic patients, mainly in a patient with ischemic cerebrovascular accident one year ago, in another patients with six ischemic strokes, and in a patient with decreased force in both legs diagnosed with diabetes and Parkinson disease. According to Niermeyer (2018), older adults with Type 2 diabetes (DM2) and hypertension (HTN) often experience cognitive weaknesses [32]. Growing evidence suggests that such weaknesses place patients at risk for gait disturbance and falls. Cognitive and gait decrements are not only common in the context of blood hypertension and DM2, but also are related to each other.

Research studies suggest an association between global cognition and postural instability/gait disturbance (PIGD) in Parkinson disease (PD), but the relationship between specific cognitive domains and PIGD symptoms is not clear. While impairments in global cognition and aspects of executive functioning were associated with more severe PIGD symptoms, specific cognitive domains were differentially related to distinct PIGD components, suggesting the presence of multiple neural pathways contributing to associations between cognition and PIGD symptoms in persons with PD [33]. Diabetic seniors also have an altered gait pattern characterized by lower velocity and stride length, and higher step width, stance time, double support time, and stride length variability compared to non-diabetic seniors [34].

Strong evidence of postural control impairments and noticeable gait deficits in diabetic peripheral neuropathy (DPN). Deterioration of somatosensory, visual, and vestibular systems with the pathologic condition of diabetes on cognitive impairment causes further instability of postural and gait performance in DPN [35].

Diabetes and language disorders

We have above reported three patients with language disorders (18%) in patients with a mixed syndrome characterized by Diabetes and Parkinson disease. In this case the language disorders were attributed to tongue tremor (18%). According to Dashtipour et al. (2018), speech impairment in PD results from a combination of motor and non-motor deficits [36]. Martnez-Sánchez (2010) termed hypokinetic dysarthria to the speech deficits featured by monopitch, mono-loudness, reduced stress, imprecise consonants, and inappropriate silences [37].

Qualitative analyses of the verbal output revealed that older subjects and diabetics produced the greatest number of previously recited words (repetitions). Repetitions may signal a failure to adequately monitor behavior which in turn could contribute to cognitive decline [38]. (Perlmuter et al., 1987). Repetitions might imply also an associated memory disorder.

Diabetes and liver and gastrointestinal diseases

We have found three patients with gastrointestinal diseases (18%). One with vowel syndrome in a patient with ischemic cerebrovascular accident, another with loss of sphincter control in a patient with diabetes and Parkinson disease (PD), and in two patients with cervicogenic headaches (CGH) and gall lithiasis and colecystitis.

The symptomatology in PD involve the autonomic nervous system at early stages in both Parkinson's disease (PD) and incidental Lewy body disease (ILBD), and affects the sympathetic, parasympathetic, and enteric nervous systems (ENS) [39,40]. The presence of α-synuclein (α-syn) aggregates in myenteric neurons throughout the digestive tract, as well as morpho-functional alterations of the enteric nervous system (ENS), have been documented in PD [41]. α-Synuclein pathology is extensively evident in the gut and appears to follow a rostrocaudal gradient. The gut may act as the starting point of PD pathology with spread toward the central nervous system. This spread of the synuclein pathology raises the possibility of prion-like propagation in PD pathogenesis [42].

We have not found previous reports on cervicogenic headaches and comorbidities with gastrointestinal diseases.

Diabetes, vertigo and dizziness

We have found vertigo and dizziness in 12% of diabetic patients. Due to chronic hyperglycemia and hyperinsulinemia patients with diabetes mellitus may have neurological deficits as peripheral neuropathy that is a debilitating micro-vascular complication affecting the proximal and distal peripheral sensory and motor nerves.

Diabetes mellitus is an independent risk factor for falling, particularly in the elderly. Due to chronic hyperglycemia and hyperinsulinemia patients with diabetes mellitus may have neurological deficits as peripheral neuropathy that is a debilitating micro-vascular complication affecting the proximal and distal peripheral sensory and motor nerves. Sensory neuropathy is prominent and represents the chief contributor to postural instability in diabetic subjects. Diabetic retinopathy is another complication consequent to a breakdown of the inner blood-retinal barrier with accumulation of extracellular fluids in the macula and growth of new vessels causing retinal detachment. Together peripheral neuropathy and retinopathy contribute to increase the risk of falls in diabetic patients, but a certain vestibular organs impairment should not be underestimated. Nevertheless, the exact mechanism and localization of peripheral vestibular damage consequent to chronic hyperglycemia and hyperinsulinemia are currently not still understood. Moreover it is not defined the possible role of these two blood conditions in worsening the prognosis of typical vestibular pathologies like "benign paroxysmal positional vertigo" and "Meniere disease". It appears plausible to hypothesize a direct connection among chronic hyperglycemic/hyperinsulinemic damage and peripheral vestibular organ dysfunction [43].

The vestibular system is complex, includes multiple structures, and is difficult and expensive to thoroughly assess. There is pathophysiologic evidence suggesting a direct effect of diabetes mellitus complications on the vestibular system, but there is limited clinical evidence regarding which specific vestibular structures are most adversely affected. Nevertheless, large population-based studies show that patients with diabetes are more likely to have vestibular loss, have a high prevalence of a specific vestibular disorder called benign paroxysmal positional vertigo, and are at a greater risk for falling [44].

The risk factors for cerebrovascular disease such as hypertension, heart disease, and diabetes were also the risk factors for central vertigo/dizziness by the chi-squared test. To predict a central origin for vertigo/dizziness, only gaze nystagmus was the significant factor by multivariate regression analysis [45].

Diabetes and diabetic neuropathy

We have reported a case (6%) with diabetes and blood hypertension showing crambs in right hemifacial region, legs, feet and arms. The pathological alteration of the nervous system in diabetic patients is extensive and frequently severe. The prevalence of the diabetic neuropathy reach high levels with the evolution of the diabetes, often showing frequencies higher than 50% in several groups of patients. The neurological lesion in this pathological situation is extensive in the diabetic patient, including widely the peripheral nervous system with its components sensory, motor and autonomic: with typical symptoms and in accordance with the pathogenesis of metabolic origin and/or microvascular disease. The autonomic nervous system is a main regulator of many systems in the human body. Then its lesion can promote significant alterations in the function of the cardiovascular, respiratory, gastrointestinal, urogenital system, that can be related to increased mortality [46].

The aetiopathogenesis of Autonomic Neuropathy (AN) results from a multifactorial process involving metabolic disorders triggered by the activation of the polyolic pathway, microangiopathy and alterations affecting the synthesis of essential fatty acids due to hyperglycemia, which is made worse by a deficient regeneration of nerve tissue. Any of the systems innervated by the autonomous nervous system can be affected; the initial symptoms are insidious and of little cause for concern until the more advanced stages of the disease. The chief dysfunctions affect the cardiovascular, digestive, genitourinary and thermoregulatory systems [47, 48].

Diabetes, neurological diseases and environment factors

The patients herein examined live in low socio-economic status, and contaminated environmental conditions. Epigenetic modifications, including DNA methylation have been identified as one mechanism by which the environment interacts with the genome and there is evidence that alterations in DNA methylation may contribute to the increased prevalence of both type 1 and type 2 diabetes. Current literature highlight the complex relationship between DNA methylation, gene expression, and the development of diabetes and related complications. Altered DNA methylation patterns in pancreatic islets, skeletal muscle and adipose tissue from subjects with type II diabetes (T2D) compared with nondiabetic controls. Environmental factors known to affect T2D, including obesity, exercise and diet, have also been found to alter the human epigenome. Additionally, ageing and the intrauterine environment are associated with differential DNA methylation. Together, these data highlight a key role for epigenetics and particularly DNA methylation in the growing incidence of T2D [49,50].

Obesity, physical inactivity and ageing increase the risk of T2D. Epigenetic modifications can change due to environmental exposures and may thereby predispose to disease. Current data support an important role for epigenetics in the pathogenesis of T2D. Numerous studies have found differential DNA methylation and gene expression in skeletal muscle, adipose tissue, the liver and pancreatic islets from subjects with T2D compared with nondiabetic controls. Nongenetic risk factors for T2D such as ageing, unhealthy diets and physical activity do also impact the epigenome in human tissues. Interestingly, physical activity altered DNA methylation of candidate genes for T2D such as THADA in muscle and FTO, KCNQ1 and TCF7L2 in adipose tissue [51].

Conclusions

The diabetic patients show blood hypertension (84%) %), cardiovascular diseases (43%), memory disorder (43%), Parkinson disease (31%), Headaches (25 %), sleep disorders (18%), gait disturbances (18%), language disorders (18%), dizziness and vertigo (12%), cervicogenic headache (12%) liver diseases (12%), gastrointestinal disease (12%) arthritis (12%), respiratory diseases (6%), Alzheimer disease (6%), and previous cerebrovascular accident (6%). Six patients with Parkinson disease, three patients with diabetes and Alzheimer disease (18%) and two cases with diabetes, blood hypertension and Alzheimer disease (12%), and two cases of diabetes and cervicogenic headaches (12%) were found. A relationship of diabetic patient lifestyle with environmental conditions, socioeconomic status and family history is postulated [52-56].

Acknowledgement

This paper has been carried out with a subvention from Castejon Foundation and the logistic support of Biological Research Institute. Faculty of Medicine. Zulia University and the Clinical Neuroscience Institute. Clinical Home San Rafael. Maracaibo Venezuela.

References

1. Tüma I (2077) Diabetes mellitus and cognitive impairments Vnitr Lek 53: 486-488.
2. Cukierman T, Gerstein HC, Williamson JD (2005) Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. Diabetologia 48: 2460-2469
3. Williamson R, McNeilly A, Sutherland C (2012) insulin resistance in the brain: An old-age or new-age problem?. Biochem Pharmacol 84: 737-745.
4. F Panza V, Frisardi, D Seripa, B P Imbimbo, D Sancarlo, et al. (2011) Metabolic Syndrome, Mild Cognitive Impairment, and Dementia. Curr Alzheimer Res 8: 492-509.
5. Vincenza Frisardi , Vincenzo Solfrizzi, Davide Seripa, Cristiano Capurso, Andrea Santamato, et al. (2010) Metabolic-cognitive Syndrome: A Cross-Talk Between Metabolic Syndrome and Alzheimer's Disease. Review Ageing Res Rev 9: 399-417.
6. Sanz C, Andrieu S, Sinclair A, Hanaire H, Vellas B et al. (2009) Diabetes is associated with a slower rate of cognitive decline in Alzheimer disease. Neurology 73: 1359-1366.
7. Barbagallo M, Dominguez LJ (2014) Type 2 diabetes mellitus and Alzheimer's disease. World J Diabetes 5: 889-893.
8. McCrimmon RJ, Ryan CM, Frier BM (2012) Diabetes and cognitive dysfunction. Lancet 379: 2291-2299.
9. Petrou M, Davatzikos C, Hsieh M, Foerster BR, Albin RL, et al. (2016) Diabetes, Gray Matter Loss, and Cognition in the Setting of Parkinson Disease. Acad Radiol 23: 577-581.
10. Bohnen NI, Kotagal V, Müller ML, Koeppe RA, Scott PJ, (2014) Diabetes mellitus is independently associated with more severe cognitive impairment in Parkinson disease.Parkinsonismo Relat Disord 20: 1394-1398.
11. Pagano G, Polychronis S, Wilson H, Giordano B, Ferrara N, et al. (2018) Diabetes mellitus and Parkinson disease. Neurology 90: e1654-e1662.
12. Umeno A, Biju V, Yoshida Y (2017) In vivo ROS production and use of oxidative stress-derived biomarkers to detect the onset of diseases such as Alzheimer's disease, Parkinson's disease, and diabetes. Free Radic Res 51: 413-427.
13. De Pablo-Fernandez E, Goldacre R, Pakpoor J, Noyce AJ, Warner TT (2018) Association between diabetes and subsequent Parkinson disease: A record-linkage cohort study. Neurology 91: e139-e142.
14. Aamodt AH, Stovner LJ, Midthjell K, Hagen K, Zwart JA (2017) Headache prevalence related to diabetes mellitus. The Head-HUNT study. Eur J Neurol 14: 738-744.
15. Hagen K, Wisløff U, Ellingsen Ø, Stovner LJ, Linde M (2016) Headache and peak oxygen uptake: The HUNT3 study. Cephalalgia 36: 437-444.
16. Shuko Takeda, Naoyuki Sato, Hiromi Rakugi, Ryuichi Morishita (2011) Molecular Mechanisms Linking Diabetes Mellitus and Alzheimer Disease: Beta-Amyloid Peptide, Insulin Signaling, and Neuronal Function. Review Mol Biosyst.
17. Aarti N Patel , Jack H Jhamandas (2012) Neuronal Receptors as Targets for the Action of Amyloid-Beta Protein (Aβ) in the Brain. Expert Rev Mol Med 14: e2.
18. Anna M Lilja, Omar Porras, Elisa Storelli, Agneta Nordberg, Amelia Marutle (2011) Functional Interactions of Fibrillar and Oligomeric Amyloid-β With alpha7 Nicotinic Receptors in Alzheimer's Disease. J Alzheimers Dis 23: 335-347.
19. Camila Fabiani, Silvia S Antollini (2019) Alzheimer's disease as a Membrane Disorder: Spatial Cross-Talk among Beta-Amyloid Peptides, Nicotinic Acetylcholine Receptors and Lipid Rafts. Review. Front Cell Neurosci 13: 309.
20. Naoyuki Sato, Shuko Takeda, Kozue Uchio-Yamada, Hironori Ueda, Tomomi Fujisawa et al. (2011) Hiromi Rakugi, Ryuichi Morishita. Role of Insulin Signaling in the Interaction between Alzheimer Disease and Diabetes Mellitus: A Missing Link to Therapeutic Potential. Curr Aging Sci 4: 118-127.
21. Dragan M Pavlović, Aleksandra M Pavlović (2008) Dementia and Diabetes Mellitus. Review Srp Arh Celok Lek 136: 170-175.
22. David Baglietto-Vargas, Jessica Shi , Devin M Yaeger Ra-

hasson Ager , Frank M LaFerla (2016) Brain Mitochondrial Dysfunction as a Link Between Alzheimer's Disease and Diabetes. Neurosci Biobehav Rev 64: 272-287.
23. Paula I Moreira, Maria S Santos, Raquel Seiça, Catarina R Oliveira (2007) Brain Mitochondrial Dysfunction as a Link Between Alzheimer's Disease and Diabetes. J Neurol Sci 257: 206-214.
24. Paula I Moreira , Ana I Duarte, Maria S Santos, A Cristina Rego, Catarina R Oliveira (2009) An Integrative View of the Role of Oxidative Stress, Mitochondria and Insulin in Alzheimer's Disease. Review. J Alzheimers Dis 16: 741-761.
25. Paula I Moreira, Ana I Duarte, Maria S Santos, A Cristina Rego, Catarina R Oliveira (2012) Alzheimer's Disease and Diabetes: An Integrative View of the Role of Mitochondria, Oxidative Stress, and Insulin. J Alzheimers Dis 30: S199-S215.
26. Dénes Zádori, Péter Klivényi, Levente Szalárdy, Ferenc Fülöp, József Toldi, et al. (2012) Mitochondrial Disturbances, Excitotoxicity, Neuroinflammation and Kynurenines: Novel Therapeutic Strategies for Neurodegenerative Disorders. Review. J Neurol Sci 322:187-191.
27. Dénes Zádori , Gábor Veres, Levente Szalárdy, Péter Klivényi, László Vécsei (2018) Alzheimer's Disease: Recent Concepts on the Relation of Mitochondrial Disturbances, Excitotoxicity, Neuroinflammation, and Kynurenines. Review. J Alzheimers Dis 62: 523-547.
28. Rodrigo O Kuljiš, Melita Salković-Petrišić (2011) Dementia, Diabetes, Alzheimer's Disease, and Insulin Resistance in the Brain: Progress, Dilemmas, New Opportunities, and a Hypothesis to Tackle Intersecting Epidemics. J Alzheimers Dis 25: 29-41.
29. Larcher S, Benhamou PY, Pépin JL, Borel AL (2015) Sleep habits and diabetes. Diabetes Metab 41: 263-271.
30. Vijay Kumar Chattu, Soosanna Kumary Chattu, Deepa Burman, David Warren Spence, Seithikurippu R Pandi-Perumal (2019) The Interlinked Rising Epidemic of Insufficient Sleep and Diabetes Mellitus. Healthcare (Basel) 7: 37.
31. Seetho IW, Wilding JP (2014) Sleep-disordered breathing, type 2 diabetes and the metabolic syndrome. Chron Respir Dis 11: 257-275.
32. Madison A (2018) Niermeyer Cognitive and Gait Decrements Among Non-Demented Older Adults With Type 2 Diabetes or Hypertension: A Systematic Review. Clin Neuropsychol 32:1256-1281.
33. V E Kelly, C O Johnson, E L McGough, A Shumway-Cook F B Horak, K A Chung , et al. (2015) Association of Cognitive Domains With Postural Instability/Gait Disturbance in Parkinson's Disease. Parkinsonism Relat Disord 21: 692-697.
34. Bruno de Souza Moreira, Rosana Ferreira Sampaio, Sheyla Rossana Cavalcanti Furtado, Rosângela Corrêa Dias, Renata Noce Kirkwood (2016) The Relationship Between Diabetes Mellitus, Geriatric Syndromes, Physical Function, and Gait: A Review of the Literature. Curr Diabetes Rev 12: 240-251.
35. Mustapa A, Justine M, Mohd Mustafah N, Jamil N, Manaf H (2016) Postural Control and Gait Performance in the Diabetic Peripheral Neuropathy: A Systematic Review. Biomed Res Int 2016: 9305025.
36. Dashtipour K, Tafreshi A, Lee J, Crawley B (2018) Speech disorders in Parkinson's disease: pathophysiology, medical management and surgical approaches. Neurodegener Dis Manag 8: 337-348.
37. Martinez-Sánchez F (2010) Speech and voice disorders in Parkinson's disease. Rev Neurol 51: 542-550.
38. Perlmuter LC, Tun P, Sizer N, McGlinchey RE, Nathan DM (1987) Age and diabetes related changes in verbal fluency. Exp Aging Res 13: 9-14.
39. Cersosimo MG, Benarroch EE (2012) Autonomic involvement in Parkinson's disease: pathology, pathophysiology, clinical features and possible peripheral biomarkers. J Neurol Sci 313: 57-63.
40. Santos-Garcia D, de Deus T, Tejera-Perez C, Exposito-Ruiz I, Suarez-Castro E, et al. (2015) Gastroparesis and other gastrointestinal symptoms in Parkinson's disease. Rev Neurol 61: 261-270.
41. Pellegrini C, Antonioli L, Colucci R, Ballabeni V, Barocelli E, et al. (2015) Gastric motor dysfunctions in Parkinson's disease: Current pre-clinical evidence. Parkinsonism Relat Disord 21: 1407-1414.
42. Mukherjee A, Biswas A, Das SK (2016) Gut dysfunction in Parkinson's disease. World J Gastroenterol 22: 5742-5752.
43. Federico Maria Gioacchini Roberto Albera, Massimo Re, Alfonso Scarpa , Claudia Cassandro , Ettore Cassandro (2018) Hyperglycemia and Diabetes Mellitus Are Related to Vestibular Organs Dysfunction: Truth or Suggestion? A Literature Review. Acta Diabetol 55: 1201-1207.
44. Erin G, Piker Daniel, J Romero (2019) Diabetes and the Vestibular System. Semin Hear 40: 300-307.
45. Yoshiyuki Ozono, Tadashi Kitahara, Munehisa Fukushima, Takahiro Michiba, Ryusuke Imai, et al. (2014) Differential Diagnosis of Vertigo and Dizziness in the Emergency Department. Acta Otolaryngol 134: 140-145.
46. Maria Cristina Foss-Freitas, Wilson Marques Junior, Milton Cesar Foss (2008) Autonomic Neuropathy: A High Risk Complication for Type 1 Diabetes Mellitus. Arq Bras Endocrinol Metabol 52: 398-406.
47. J Bruna , X Navarro (2005) Autonomic Neuropathy in Diabetes Mellitus. Rev Neurol 40: 102-110.
48. Wolfgang H Jost (2003) Autonomic Dysfunctions in Idiopathic Parkinson's Disease. J Neurol 1: I28-I30.
49. Tina Rönn , Charlotte Ling (2015) DNA Methylation as a Diagnostic and Therapeutic Target in the Battle Against Type 2 Diabetes. Epigenomics 7: 451-460.
50. Amita Bansal, Sara E Pinney (2017) DNA Methylation and Its Role in the Pathogenesis of Diabetes. Pediatr Diabetes 18: 167-177.
51. C Ling (2020) Epigenetic Regulation of Insulin Action and Secretion - Role in the Pathogenesis of Type 2 Diabetes. J Intern Med 13049.
52. Cukierman T, Gerstein HC, Williamson JD (2005) Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. Diabetologia 48: 2460-2469.
53. Sanz C, Andrieu S, Sinclair A, Hanaire H, Vellas B, et al. (2009) Diabetes is associated with a slower rate of cognitive decline in Alzheimer disease. Neurology 73: 1359-1366.
54. Barbagallo M, Dominguez LJ (2014) Type 2 diabetes mellitus and Alzheimer's disease. World J Diabetes 5: 889-893.
55. Perlmuter LC, Tun P, Sizer N, McGlinchey RE, Nathan DM (1987) Age and diabetes related changes in verbal fluency. Exp Aging Res 13: 9-14.
56. Linong Ji, Dayi Hu, Changyu Pan, Jianping Weng, Yong Huo, et al. (2013) Primacy of the 3B Approach to Control Risk Factors for Cardiovascular Disease in Type 2 Diabetes Patients. Am J Med 126: e11-22.