

Scientific Research and Essays

Volume 11 Number 14 30 July 2016
ISSN 1992-2248



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Muhammad Firman Akbar

Full Length Research Paper

Exploring the association between diabetes mellitus and hearing loss: Genetic mutation, neuropathy and microangiopathy

Muhammad Firman Akbar

Department of General Health Service, Sahabat Sehat Clinic, Jl Pariwisata No.16 Batu Layar, 83551 Lombok Barat, Nusa Tenggara Barat, Indonesia.

Received 16 May, 2016; Accepted 14 July, 2016

Diabetes mellitus (DM) has progressively increased in global prevalence. Recent studies have found that patients with DM may suffer from hearing impairment as a chronic complication. The effect of hearing loss may impair the quality of life of patients which affects functional, social, as well as psychological aspects. Both DM and hearing loss are considered to be associated, although this correlation remains elusive. There are three theories proposed to establish the association, which are microangiopathy, neuropathy and genetic mutation in mitochondrial DNA (mtDNA). This essay will initially discuss the importance of mtDNA mutations and neuropathy, as well as microangiopathy, in developing the expression of deafness in diabetes mellitus. It will also consider the limitation of these respective theories to explain the mechanism of hearing loss in diabetes mellitus patients.

Key words: Diabetes mellitus, hearing loss, mtDNA mutation, microangiopathy, neuropathy.

INTRODUCTION

Diabetes mellitus (DM) has progressively increased in global prevalence (Chen et al., 2012). DM has recently been of considerable concern for public health since its complications increase morbidity and mortality in patients; even studies have also found that patients with DM may suffer from hearing impairment (Powers, 2015a). Hearing loss is a more common issue in public health nowadays and it is prevalent in approximately two-thirds of the geriatric population (>70 years) (Bainbridge and Wallhagen, 2014). The effect of hearing loss may impair the quality of life of patients which affects functional, social, as well as psychological aspects (Ciorba et al.,

2012). Moreover, a systematic review by Horikawa et al. (2013) which was obtained from various relevant cross-sectional studies with over 20,000 participants had shown that higher prevalence of hearing impairment in diabetics than that of in non-diabetics was persistent. The incidence of hearing loss in diabetic patients is the highest (62%), compared to tinnitus and vertigo (Padhy, 2014). Young adults with type 1 DM have shown slight abnormalities of qualitative perception in comparison with normal controls.

These abnormalities may suggest microvascular or neuropathic changes (Lasagni et al., 2015). In a cohort

*Corresponding author. E-mail: m.f.akbar@dr.com. Tel: +62 838 753 01202.

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study, patients with uncontrolled type 2 DM have poorer hearing impairment and tend to have a greater risk of retinopathy, compared to healthy controls and controlled diabetes (Konrad-Martin et al., 2015). Both DM and hearing loss are considered to be associated. Nevertheless, this correlation remains elusive (Oh et al., 2015). There are three theories proposed by scientists to establish the association, which are microangiopathy, neuropathy and genetic mutation in mitochondrial DNA (mtDNA). However, the latter has stronger and more marked data which may lead to unraveling of the occurrence of hearing loss in diabetic patients. This essay will initially discuss the importance of mtDNA mutations and neuropathy, as well as microangiopathy, in developing the expression of deafness in diabetes mellitus. It will also consider the limitation of these respective theories to explain the mechanism of hearing loss in diabetes mellitus.

MITOCHONDRIAL DNA MUTATION

Firstly, both DM and hearing loss share the same etiology regarding whether or not mitochondria within cells work. In their literature review, Kim et al. (2008) have revealed that mitochondrial dysfunction affects the ratio of ATP (adenosine triphosphate) production/oxygen consumption, thereby resulting in an increase of ROS (reactive oxygen species) production. It is understood that a marked elevation of ROS may cause insulin resistance in tissues, which means that the risk of DM is consequently higher. Furthermore, mitochondrial dysfunction also occurs in hearing loss patients with a defect in mtDNA (mitochondrial DNA). Yamasoba et al. (2007) argued in their review that the accumulation of mtDNA mutations/deletions may have an impact on the development of age-associated hearing loss through decreasing energy metabolism and declining the function of respiratory chain.

In addition, other results supporting the role of mtDNA in both diseases was initially reported in 1992 by van den Ouweland et al. (1992) who found in their pedigree, biochemical and mitochondrial DNA analyses that 3243A>G mutation of the tRNA^{Leu(UUR)} gene expressed the deficiency of aminoacylation of tRNA^{Leu(UUR)}, thereby resulting in depleted protein synthesis in mitochondria as well as influencing the function of cell respiration. A subsequent study in 1994 by van den Ouweland et al. revealed that this mutation is a new variation of diabetes which also co-presents deafness, known as maternally inherited diabetes and deafness (MIDD) (van den Ouweland et al., 1994).

Furthermore, other evidence derived from a molecular genetic study of a 40-years old Tunisian male showing the role of mtDNA mutation in MIDD has been discovered by Mezghani et al. (2013) who investigated other alternative mutations in addition to the 3243A>G

tRNA^{Leu(UUR)} gene mutation. They found multiple deletions of 1555A>G in 12S rRNA and 3308T>C in ND1 genes. The 1555A>G 12S rRNA mutation is commonly seen in deafness cases, but it had been not reported in maternally inherited diabetes and deafness (MIDD). In addition, the mutation of the ND1 gene may interfere with the function of ND1 protein which plays an important role in transferring electrons from NADH (nicotinamide adenine dinucleotide plus hydrogen) to ubiquinone. In the same year, Mkaouar-Rebai et al. (2013) also published the results of molecular genetic study of a 14-years old Tunisian girl with MIDD affected by the occurrence of mutational mtDNA. Interestingly, they firstly screened the region of tRNA^{Leu(UUR)} and 12S rRNA genes but did not find a significant result. Furthermore, they screened the tRNA^{Ser(UCN)} gene because it usually occurs in mutations expressing deafness. The mutational lesion of 7444G>A in the mitochondrial COI/precursor gene was revealed in this study and with further analysis, it also showed a novel variation of the 6498C>A mitochondrial COI gene. How the genes discovered by Mkaouar-Rebai et al. (2013) can express MIDD is still elusive, but a possible mechanism is by affecting the function of oxidative phosphorylation complex IV and ultimately resulting in mitochondrial dysfunctions.

Moreover, some studies revealed that the prevalence of MIDD varied in 0.5 to over 2.5% of diabetics (Guillausseau et al., 2001). Maassen (1994) concluded that in the pedigree analysis in a population consisting of 473 diabetics, the prevalence of MIDD in the Netherlands is less than 0.5%. In Japan, the prevalence of this mitochondrial gene mutation was higher, around 1% of diabetic-diagnosed patients (Katagiri et al., 1994). Screening of MODY (maturity onset of diabetes of young) and mitochondrial mutations in total 115 Finnish and Swedish families by Lehto et al. (1999) resulted that the prevalence of MIDD was 2.6%. More recently, An epidemiological study by Martikainen et al. (2013) consistent with previous prevalence, showed that the prevalence of MIDD is approximately 1% among young adults. In addition, the UK MRC Mitochondrial Disease Patient Cohort Study had shown that of 129 patients, 53% was determined to have 3243A>G mutation, and 30% of which was contributed by MIDD case (39 patients).

NEUROPATHY

Other perspective comes from the theory of microvascular complications of DM which refers to diabetic neuropathy. The prevalence of peripheral neuropathy is much higher particularly in older population, with one of which predictors is a history of diabetes mellitus. In almost 800 elderly people, at least 26% of the population has one bilateral sensory impairment (Mold et al., 2004). Diabetes can affect

various types of nerve fibers among autonomic, sensory and motor neurons, attacks either small or large fibers and occurs commonly as distal symmetrical polyneuropathy (DSP). Although diabetes characteristically presents with chronic hyperglycemia, the mechanism of its complications, including diabetic neuropathy, remains elusive. Nonetheless, there are four proposed theories which molecularly explain the pathomechanism, one of which describes the occurrence of diabetic neuropathy, in which hyperglycemia accumulates diacylglycerol formation, thereby activating protein kinase C (PKC). This pathway is very important since PKC plays a significant role in the transcription of genes responsible for contractile proteins, fibronectin, type IV collagen, and extracellular matrix (ECM) proteins in neurons and endothelial cells (Powers, 2015b). Thus, diabetic neuropathy-affected neurons are characteristically presented as progressively degenerated axons, which as a consequence, can clinically alter the amplitude of sensory as well as motor responses, and as demyelinated neurons due to hyperglycemia, leading to a reduction in nerve conduction velocity (David et al., 2015).

Despite the fact that the most common manifestation of diabetic neuropathy occurs as DSP, cranial nerves may also be affected. There are some reports that cranial nerves, particularly the third nerve (oculomotor), are involved as either single or multiple mononeuropathy and presents neurological manifestations such as ophthalmoplegia, ptosis and Bell's palsy, depending on the fibers involved (Powers, 2015b). Moreover, the role of neuropathy in the development of hearing loss in patients with diabetes is also documented (David et al., 2015). The National Health and Nutrition Examination Survey (NHANES), involving over 1500 participants who were completing the audiometric testing, from 40 to 69 years old, concluded the possible mechanism of diabetic-associated hearing loss in the U.S population. They argued that neuropathy is a possible theory explaining the pathomechanism and mediating hearing loss and DM (Bainbridge et al., 2010).

There are some studies which have explored the role of neuropathy in DM-associated hearing impairment. In various literature reviews, there are some histopathological lesions, including neural destruction and microglial activation, in vestibulocochlear nerves due to hyperglycemia. These changes resulted from oxidative stress and dendritic damage, which ultimately resulted in an elevated level of reactive oxygen species (ROS) (Brownlee, 2001; Sonnevile et al., 2012; Hinder et al., 2012; Helzner and Contrera, 2016). This evidence is a proof that there is a reduction of neurological transmission in affected neurons. In addition, other evidence supporting this theory comes from testing of the ABR (auditory brainstem response).

The aim of ABR testing is to assess evoked potential waves resulted by the auditory pathway, which likely

determines the integrity of neural brainstem generators. The interpretations are resulted from waves I-V and reflect the sound transmission from olivary nucleus, cochlear nuclei, inferior colliculi and lateral lemniscus of vestibulocochlear nerve (Helzner and Contrera, 2016; Kavanagh and Beardsley, 1979; Bayazit et al., 2000). A study by Bayazit et al., which assessed 79 diabetic patients (59 with and 20 without complications, respectively) with audiometry and auditory brain stem response (ABR), resulted that the latencies of study group were markedly prolonged in comparison to control group. This result is consistent with other study by Vaughan et al., who assessed 791 patients and significantly found that there were latency differences between diabetic and non-diabetic populations (Helzner and Contrera, 2016; Bayazit et al., 2000; Vaughan et al., 2007).

MICROANGIOPATHY

In several trials, hyperglycemia has been identified to have an important role in the development of vascular complications. Some hypotheses have been proposed to determine the mechanism of hyperglycemia affecting the vascular function. PKC activation, polyol pathway activity, glucose oxidation and AGE (advanced glycation end product) production are popular pathways causing microangiopathy, leading to endothelial dysfunction through an increasing ROS production (Powers, 2015b; Hadi and Suwaidi, 2007; Goldin et al., 2006). Diabetic microangiopathy, defined as an angiopathy occurring in small blood vessels and characteristically demonstrates an accumulation of intimal glucoprotein, endothelial proliferation and basal membrane thickness, has been documented to occur in internal auditory artery lumen (Maia and de Campos, 2005).

Several studies were documented to support microangiopathy to associate hearing impairment and diabetes. According to epidemiological concepts by Yamasoba et al. (2013) risk factors of hearing loss are determined into 4 categories, and one of which is health co-morbidities vascular sclerosis. In addition to neuropathy and inflammation, Bainbridge et al. (2010) also proposed that microangiopathy and hyperglycemia may play pivotal roles as potential mediators of hearing loss in diabetic population. Moreover, animal studies from several decades ago have experimented the impact of diabetes in inner ear. Rats with alloxan- or streptozocin-induced diabetes were observed and the results led to thickening of basal membrane of vascular striae and loss of outer hair cells (Maia and de Campos, 2005; Costa, 1967; Smith et al., 1995; Raynor et al., 1995). In their literature review, David et al. (2015) argued that these abnormalities are likely due to disruption of blood supply to the cochlea, reduction of blood flow in affected vessels, or vestibulocochlear nerve degeneration.

THE LIMITATIONS OF RESPECTIVE THEORIES

Although inner ear organ is rich of vasculature and nerve, microangiopathy and neuropathy have also some limitations to explain the link between hearing loss and DM. Until recently, there is no consistent result whether microangiopathy or neuropathy can explain the mechanism. Maia and de Campos (2005) presented lists of studies from 1950 to 2003 that both did and did not support the role of neuropathy and microangiopathy in DM-associated hearing loss, which were 11 and 5 studies, respectively. Moreover, there also remains controversy regarding the etiology of hearing loss in diabetes. Some researchers have claimed that microangiopathy proves the association of hearing loss and diabetes. On the other hand, some researchers argued that neuropathy may dominate the development of hearing loss in DM (David et al., 2015; Helzner and Contrera, 2016).

Moreover, although genetic mutation in mtDNA is mainly considered to have a significant association between hearing loss and diabetes mellitus, this theory has some limitations. Firstly, it is widely accepted that DM has been classified into type 1, type 2, gestational and other specific types of diabetes mellitus. This classification places mtDNA mutation as the specific etiology of DM (American Diabetes Association, 2013; Powers, 2015b). It only provides a clear explanation of genetic cause of DM, and whether it is able to explain the mechanism of chronic hyperglycemia consequently causing hearing loss in all types of DM remains elusive. Furthermore, the genetic mutation of mtDNA discovered by van den Ouweland et al. (1992) still cannot provide the answer as to why 3243A>G tRNA^{Leu(UUR)} gene mutation occurs in two different diseases, which are MIDD and MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome. Finsterer et al. (2015) have documented some evidences with respect to the occurrence of 3243A>G tRNA^{Leu(UUR)} gene mutation which manifests in other genetic diseases. It is notable that the 3243A>G mtDNA mutation causes Leigh syndrome, non-syndromic enteromyopathy, Kearns-Sayre syndrome (KSS), floppy infant syndrome, MELAS - myoclonic epilepsy and ragged red fibers (MERRF) overlap syndrome, chronic progressive external ophthalmoplegia (CPEO), and other non-syndromic mitochondrial disorders (MIDs). In addition, although the majority of MIDD cases is mainly caused by the tRNA^{Leu(UUR)} gene mutation, other mutated genes, such as the COXIII, 12S rRNA, ND1 genes, etc, have also been reported as causes of MIDD. Whether these genes have the same molecular mechanism in developing maternally inherited diabetes and deafness remains unclear.

However, as Maia and de Campos pointed out, there is an increasing concern towards hearing impairment due to genetic causes, particularly to mtDNA mutations. Interestingly, MIDD, firstly identified by van den

Ouweland in 1994, has marked results of investigations in the recent decade, aggregating to nearly 2% diabetic cases in Japan as well as the Netherlands. There is less skepticism to a point that genetic causes are the most reasonable answer to some questions about the association hearing impairment and diabetes mellitus (van den Ouweland et al., 1994; Maia and de Campos, 2005; Kakarlapudi et al., 2003).

Indeed, genetic involvement has been considered as a strong correlation between diabetes and its complications, including hearing loss. Among the most common diabetic complications, some susceptible genes have been proposed to be independent factors, despite the duration of diabetes and HbA1c level. For instances, in a cohort, case-control and genotype-phenotype correlation study involving over 320 patients, TCF7L2 gene was significantly associated with diabetic retinopathy and autonomic neuropathy of cardiovascular diseases (Ciccacci et al., 2013). In addition, genetic linkage and characteristic analyses resulted that genes responsible for lipoprotein metabolism, PPARs (Peroxisome proliferator-activated receptors), cytokines, chemokines, and KLFs (Krüppel-like family of transcription factors) associated type 2 DM and coronary heart disease (Akbar, 2015). Moreover, Nazir et al. (2014), in their meta-analysis of previous 34 studies, resulted 11 susceptible genes which had important roles in diabetic nephropathy through GPCR signaling, receptor binding pathways and the development of chronic renal disease.

CONCLUSION

In conclusion, although some investigators have argued that the association between DM and hearing loss remains unclear, it is scientifically accepted that a genetic perspective on identifying the association seems promising. Moreover, mutation in mitochondria provides more evidence than either neuropathy or microangiopathy does in terms of exploring the linkage between diabetes mellitus and hearing loss. However, whether the mitochondria mutation is able to present the same pathology in all types of diabetes is less understood. Thus, further investigations must be conducted to provide a clear explanation of the role of in hearing loss and diabetes mellitus.

Conflict of Interests

The author has not declared any conflict of interests.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit

sector.

ACKNOWLEDGEMENTS

The author expresses his thanks to Australia Awards Indonesia and Joanne Sweeney for language supports.

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