Journal of Molecular and Genetic Medicine

Benlier, J Mol Genet Med 2019, 13:1
DOI: 10.4172/1747-0862.1000400

Short Communication Open Access

Methylglyoxal Levels and Restless Leg Syndrome in Patients with Chronic Renal Failure

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Abstract

Restless leg syndrome occurs frequently among patients with end-stage renal disease. Although the etiopathogenesis of restless leg syndrome has not been fully elucidated, advanced age, female gender, positive family history, chronic renal failure, pregnancy and folic acid and iron deficiency have all been implicated. Recent studies found a diminished ability of D2 receptors to bind ligands and reduced 18F-dopa uptake in the putamen and striatum in patients with restless leg syndrome. A marked increase in the plasma concentrations of glycation end-products was observed in uremic patients. Methylglyoxal is a major end-product of glycolysis. Methylglyoxal is a reactive carbonyl species that is formed during glucose metabolism. Methylglyoxal may increase the dopamine concentration and other toxic metabolites such as salsolinol in dopaminergic neurons and dopamine-mediated oxidative stress could contribute to damage of dopaminergic neurons.

Keywords: Chronic renal failure; Restless; Methylglyoxal

Introduction

End-Stage Renal Disease (ESRD) is associated with high morbidity and mortality rates and increasing incidence both in Turkey and globally and has considerable negative effects on quality of life of affected patients. Accordingly, ESRD is considered as a global public health problem because of the high cost of required for renal replacement therapies and its poor prognostic course [1,2]. Annually, ESRD occurs in approximately 1000 people per million and this number is estimated to increase by more than 2-fold over the next decade [3].

End-stage renal disease (ESRD) is a clinical picture characterized by a glomerular filtration rate (GFR) below 15 ml/min, irreversible loss of endogenous renal function and the need for initiation of kidney replacement therapy (hemodialysis, peritoneal dialysis or transplantation) to prevent life-threatening uremia [4].

According to the data from the United States Renal Data System (USRDS), 65.0% of ESRD patients are treated with hemodialysis and the National Nephrology, Dialysis and Transplantation Registry Report of the Turkish Society of Nephrology (TND) documented that 76.12% of these patients are on hemodialysis treatment and 4.7% are on continuous ambulatory peritoneal dialysis treatment [5,6]. By the end of 2016, the individuals aged between 45 and 64 years constituted the majority of patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) treatment [6].

Restless leg syndrome

Restless leg syndrome is a condition characterized by symptoms of unpleasant paresthesia and burning sensation and an irresistible urge to move extremities (most often legs) at rest and during nighttime. Typically, symptoms occur during periods of limb inactivity which worsen at night and during sleep [7-9]. In 1995, the International Restless legs Study Group has proposed the following four criteria for the diagnosis of restless leg syndrome: 1) an urge to move the extremities, often associated with paresthesias and dysesthesias, 2) worsening of symptoms at rest with at least temporary relief by activity, 3) motor restlessness and relief with movement (walking, rubbing, massaging) and 4) worsening of symptoms in the evening or night (10). Restless leg syndrome has a prevalence that ranges from 2% to 12% in the general population and 6% to 62% among hemodialysis patients [10-13]. Advanced age, female gender, positive family history, chronic renal failure, pregnancy and folic acid and iron deficiency have been reported as predisposing factors (10). While several theories were proposed to explain the exact cause and pathophysiology of restless leg syndrome, none of them led to conclusive evidence. Restless leg syndrome causes major distress in patients including sleep disorders and impaired quality of life [10,14].

The observations of increased occurrence of restless leg syndrome symptoms with dopamine antagonists that cross the blood-brain barrier and no change in RLS symptoms with dopamine antagonists that do not cross the blood-brain barrier suggest that the central nervous system (CNS) is mostly involved in the restless leg syndrome [15]. Positron emission tomographic studies have shown a reduction in D2 receptors and decreased 18F-dopa uptake in several areas of the brain in patients with restless leg syndrome [16,17].

Advanced glycation end products and Methylglyoxal

Advanced glycation end-products (AGEs) were first identified by Maillard in 1912 who observed "a browning reaction" in cooked food. AGEs are formed through complex, sequential non-enzymatic reactions. They are a group of heterogeneous compounds that are formed by the non-enzymatic glycation process involving covalent attachment of carbonyl groups of reducing sugars to free amino groups of proteins, lipoproteins or nucleic acids [18]. This reaction evolves slowly through various steps, eventually leading to changes at the molecular level. Advanced glycation end-products are formed under physiological conditions and accumulate with increasing biological age [19]. The formation and accumulation of AGEs are involved in

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Received February 06, 2019; **Accepted** February 13, 2019; **Published** February 20, 2019

Citation: Benlier N (2019) Methylglyoxal Levels and Restless Leg Syndrome in Patients with Chronic Renal Failure. J Mol Genet Med 13: 400 doi:10.4172/1747-0862.1000400

the pathophysiology of numerous disorders and poor prognosis. A marked increase in the plasma concentrations of AGEs was observed in uremic patients [20]. AGEs were found to accumulate in the nerve tissues in neurodegenerative disorders and increased plasma levels were observed in chronic pulmonary diseases [21].

Discussion

Major advanced glycation end-products include Nε-fructosyl-lysine (FL) and dicarbonyl metabolites methylglyoxal, glyoxal, and 3-deoxyglucosone (3-DG) [22]. 35 to 90% of AGEs are eliminated by the kidneys and the resulting kidney damage causes accumulation of AGEs. Methylglyoxal is an endogenous byproduct of glucose metabolism and a reactive carbonyl species that is generated by the non-enzymatic fragmentation of dihydroxyacetone phosphate and glyceraldehyde-3-phosphate [23,24].

The glyoxalase enzymes (glyoxalase-I (Glo-I) and glyoxalase-II (Glo-II)) were discovered in 1913 by the research groups of Dakin-Dudley and Neuberg [25]. Methylglyoxal is metabolized by the enzyme glyoxalase 1 (GLO1) [26].

Methylglyoxal directly damages neurons by increasing reactive oxygen species (ROS) production and by inhibiting mitochondrial respiration [27]. Previous studies showed that mitochondrial dysfunction and increased oxidative stress are involved in the neuronal cell death in Parkinson's disease [28,29]. Another study found that methylglyoxal may increase the dopamine concentration and other toxic metabolites such as salsolinol in dopaminergic neurons and dopamine-mediated oxidative stress could contribute to damage of dopaminergic neurons.

Conclusion

Data from aforementioned studies suggest that the etiopathogenesis of restless leg syndrome, a common disorder affecting patients with chronic renal failure, might also be associated with methylglyoxal level and may provide further insight into the understanding of the potential relationship.

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