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CASE REPORT

Clinical and Molecular Characteristics of A Novel Homozygous *DNAJC3* Gene Variant in a Saudi family

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SUMMARY

Combined cerebellar and peripheral ataxia with hearing loss and diabetes mellitus is an extremely rare neurodegenerative disorder affecting the central and peripheral nervous systems. The pathogenesis of widespread neurodegeneration in previously reported cases with homozygous*DNAJC3*mutations is proposed to be caused by a common etiology that is mitochondrial dysfunction and loss of mitigation of the endoplasmic reticulum stress response. In this paper, we reported a rare case of combined cerebellar and peripheral ataxia with hearing loss and diabetes mellitus in a Saudi family with a novel homozygous stop-gain mutation c.1177C>T p.(Arg393*) in exon 10 of the *DNAJC3* gene, which creates a premature stop codon.The advances in genetic testing, including whole exome sequencing, have increased our knowledge of mitochondrial disorders, monogenic diabetes, and homozygous *DNAJC3*mutations phenotype who presents with juvenile-onset diabetes mellitus and multiple symptoms and signs of neurodegenerative disease, *DNAJC3*mutation should be suspected.
Keywords: *DNAJC3*; Combined Cerebellar and Peripheral Ataxia with Hearing Loss and Diabetes Mellitus; Autosomal Recessive; Mutation; Saudi Arabia.

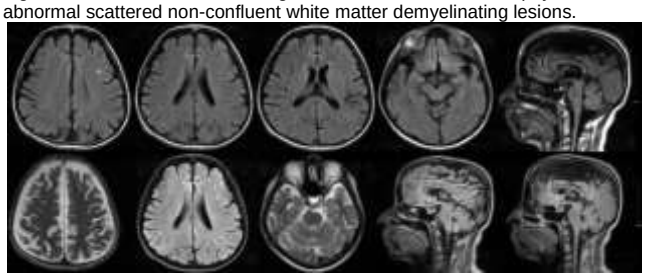
INTRODUCTION

Mitochondrial function is an essential regulator of cell death and an important prerequisite for normal insulin secretion and pancreatic response[1]. Subsequently, mitochondrial dysfunction may cause neurodegenerative disorders and insulin resistance/pancreatic beta-cell dysfunction[2]. Although diabetes mellitus and neurodegeneration are still not well known or understood, one of the rare genetic mutations causing both disorders are related to the loss of the Bip(immunoglobulin heavy chain binding protein) co-chaperone *DNAJC3*[3]. In this paper, we report a novel homozygous pathogenic variant in the *DNAJC3*gene in two siblings from a Saudi Bedouin family who presented with diabetes mellitus and multisystem neurodegenerative disease. We are not only reporting a rare genetic mutation, but we present an interesting neuroimaging, new clinical feature (epilepsy), and review the related literature of the genetic pathophysiology.

CASE REPORT

A 31-year-old male was referred to the neurology clinics for evaluation of multiple neurological complaints including seizures. He was diagnosed with diabetes mellitus at the age of 4 years and was treated using insulin regimens. He was born to consanguineous parents from a Saudi Bedouin family at full term and spontaneous vaginal delivery. He belonged to a large family with 7 sisters and 2 brothers with only one sister having a similar phenotype. This was one deceased sibling with global developmental delay, seizures, hypoglycemia, visual impairment, and metabolic acidosis. One other sister was diagnosed with diabetes mellitus at the age of 30. His mother was healthy and his father had diabetes and hypertension. Since birth, our patient was found to have syndactyly, bifid thumb, and pectus carinatum at birth. Over the years, he developed multiple medical disorders including hypothyroidism, global developmental delay, short stature, hearing loss, heart failure, and intellectual disability. Neurologically, apart from developmental delay, short stature, and being wheelchair-bound, he exhibited marked cognitive impairment with a mini-mental status scale score of 23/30 and multiple focal neurological deficits and long-tract findings including bilateral sensorineural hearing loss, weakness in all limbs, bilateral Babinski sign, sensory ataxia, and lower limb areflexia. Chromosomal microarray analysis was performed a few years ago, which did not reveal any copy number variants. Whole exome sequencing revealed a homozygous stop-gain mutation c.1177C>T p.(Arg393*) in exon 10 of the *DNAJC3* gene, which creates a premature stop codon. As part of his workup, an MRI of the brain revealed cerebral and cerebellar atrophy with abnormal scattered non-confluent white matter demyelinating lesions (Figure 1). Nerve conduction study showed length-dependent mixed demyelinating and axonal sensorimotor neuropathy. His different endocrinopathies were treated with different medications including oral hypoglycemic agents and thyroxine replacement therapy. He was started on aspirin and metoprolol for his cardiac dysfunction. Seizures were controlled with lamotrigine 50mg twice daily. Genetic counseling was provided to the family.

Figure 1: MRI of the brain showing cerebral and cerebellar atrophy with abnormal scattered non-confluent white matter demyelinating lesions.



DISCUSSION

Neurons are extremely sensitive structures that are vulnerable to toxicity induced by aggregated oligomers and proteinaceous inclusions. They depend heavily on this intrinsic network of protein quality control mechanisms designed to maintain proteostasis. Proteostasis is defined as a state in which all proteins in the proteome are in the conformation, concentration, and location that are required for a correct functioning of the cell. Cells, including neurons, have several mechanisms to regulate the biogenesis, folding, trafficking, or degradation of proteins to ensure proteostasis and prevent diseases related to an imbalance in protein folding[4]. Among the causes of this imbalance in protein folding are mutations or stresses. Cells, including neurons, respond to stresses through compartment-related signaling

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pathways. These compartment-related signaling pathways include heat shock response, which mediates a transcriptional response to stress through heat shock factors whereas the endoplasmic reticulum has the unfolded protein response. The heat shock proteins and the unfolded protein response reduce protein translation and activate signaling pathways that increase the production of protective factors, hence restoring protein homeostasis[5].

In post-mitotic cells, including neurons, maintenance of protein homeostasis is vital. Neurons possess a complex network of proteins that are highly dedicated to controlling protein quality and maintaining protein homeostasis (proteostasis). Among these highly specialized proteins, molecular chaperones maintain proteostasis by binding and shielding hydrophobic regions of nascent or misfolded proteins. In addition, it allows correct folding and conformational changes and enable quality control. There are many different families of molecular chaperones. The largest of which is the DNAJ family. This family is defined by the J domain, which regulates the function of heat shock protein 70. The proteins of this family can also have multiple other protein domains leading to diverse and specific roles in the cell, including targeting client proteins for degradation via the proteosome, chaperone-mediated autophagy, and uncoating clathrin-coated vesicles[6].

The DNAJC3 is a 58 kDa protein that is targeted to the cytoplasmic face of the endoplasmic reticulum. It is present in all tissues, including the nervous system, with predominance in the pancreatic cells, including beta cells and hepatocytes. It can also bind and inhibit the unfolded protein response sensor PERK in the endoplasmic reticulum. It is thought that this binding has a role in regulating the unfolded protein response. Finally, *DNAJC3* can recruit cytosolic heat shock protein 70 to the face of the endoplasmic reticulum and work with SEC61 as part of the translocation machinery[7]. The end result of knocking down this protein result in the accumulation of misfolded protein in the endoplasmic reticulum, activation of the unfolded protein response, and decreased ability to cope with endoplasmic reticulum stress. Mutations in *DNAJC3* cause multisystem neurodegeneration and diabetes mellitus[8].

Combined cerebellar and peripheral ataxia with hearing loss and diabetes mellitus is an extremely rare neurodegenerative disorder affecting the central and peripheral nervous systems. The first detailed description of this disorder was published by Synofzik et al[3] in 2014 who reported two families with juvenile-onset insulin-dependent diabetes mellitus, short stature, and several neurological abnormalities including combined cerebellar and afferent ataxia, demyelinating sensorimotor polyneuropathy, sensorineural hearing loss, and mild upper motor neuron damage. The mode of inheritance in the families reported by Synofzik et al[3] was consistent with an autosomal recessive pattern. The five affected cases were born to consanguineous parents (one family was Turkish and the other one was identified through a German registry search of individuals with diabetes). Subsequently, few patients were reported with homozygous *DNAJC3* mutations. The pathogenesis of widespread neurodegeneration in these cases is proposed to be caused by a common etiology that is mitochondrial dysfunction and loss of mitigation of the endoplasmic reticulum stress response[9].

Our patient developed seizures, which responded well to a small dose of lamotrigine. Seizures were not reported before as part of the clinical features of mutations in the *DNAJC3*. Seizures can be explained in a similar way to other clinical features of neurodegeneration. Mutations in the *DNAJC3* cause inability to activate unfolded protein response. As a result, the protein folding capacity of the endoplasmic reticulum is down regulated with increased protein translation and reduced degradation of misfolded proteins. With this inability to remedy the protein folding defects, the pro-adaptive unfolded protein response signaling is not shifted toward a pro-apoptotic pathway. The consequent pathological process results in neuronal apoptosis with resulting epilepsy[10].

CONCLUSION

We reported a rare case of combined cerebellar and peripheral ataxia with hearing loss and diabetes mellitus in a Saudi family with a novel homozygous stop-gain mutation c.1177C>T p.(Arg393*) in exon 10 of the *DNAJC3* gene, which creates a premature stop codon. The advances in genetic testing, including whole exome sequencing, have increased our knowledge of mitochondrial disorders, monogenic diabetes, and homozygous *DNAJC3*mutations phenotype who presents with juvenile-onset diabetes mellitus and multiple symptoms and signs of neurodegenerative disease, *DNAJC3* mutation should be suspected.

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Author contribution: MIN & BS: Designed and experiments. MIN, BS & HA: Conducted and experiments. Analysed the data and wrote the manuscript and revised the manuscript. All authors agree to be responsible for all aspects of their research work.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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