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First Case Report of *MEF2C* Gene Mutation Syndrome (Rett Phenotype) in Libyan Pediatric Population

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Abstract **Case Report**

Myocyte enhancer factor 2C *(MEF2C)* gene mutation syndrome is an extremely rare neurodevelopmental disorder with only 117 cases are documented in the current literature across the globe. We hereby document the first Libyan case report in a male child on clinical background of a global developmental delay and stereotypic behaviors. The diagnosis was confirmed utilizing Whole Exon Sequencing that showed a heterozygous deletion involving exons 1-2 of the *MEF2C* gene. Neurological features including global developmental delay, impaired language function, hypotonia, delayed cross motor skills and seizure, are common among affected children. Patients with *MEF2C* also exhibit several features of Rett Syndrome such as, autism, mannerism and various stereotypic behaviors. That make it difficult to differentiate between the two conditions based on just clinical background.

Keywords: Gene Mutation, Developmental Delay, Rett Syndrome, Autism.

INTRODUCTION

Myocyte enhancer factor 2C *(MEF2C)* Haploinsufficiency syndrome is an extremely rare rather being a newly emerging neurodevelopmental disorder [1]. Certainly, a recent systemic review study revealed there is only 117 patients over the globe are being diagnosed with the condition [2]. It is considered a genetic disease owing to its linkage to microdeletions of chromosome 5q14.3-5q15, which is involving *MEF2C* gene in common [3].

MEF2C syndrome was initially discovered in 2008 by Dr. Stuart Lipton and his research team at Sanford-Burnham Medical Research Institute utilizing murine model of mutated gene [4]. Interestingly, *MEF2C* knocked out mice showed abnormal brain tissues and exhibited a wide spectrum of various neurological and behavioral changes, including severe autistic features [5]. A year later, in 2009 Dr. Hartmut Engels and his team from the German Institute of Human Genetics [6], described the condition on three unrelated patients who were presented with sever psychomotor retardation, muscular hypotonia, seizure and various brain anomalies. In the current report study, we document the first national report of this rare neurodevelopmental disorder in a Libyan male child aged 4 years.

CASE REPORT

Yahia was born on 29th of March 2020 of non consequent parents. He presented to Neurology Clinic with a history of global developmental delay, most noticeably speech and language development, along with delayed gross motor milestones. Indeed, Yahia was able to walk by only age of two and half years. No clear history of developmental regression was noticed by the parents. Yahia also has had some autisitic features, including poor social skills and repetitive behavior. By age of three years, he developed seizure and was diagnosed with generalised tonic clonic epilepsy. Perinatal history was remarkable for early floppiness, feeding difficulties and poor eye contact.

Clinically, Yahia was mentally subnormal and exhibited some autisitic features, along with delay in all developmental milestones. He also displayed repetitive purposeless hand movements (Fig 1). Other examinations including head circumference were unremarkable, a part of subtle dysmorphic features, including high and wide forehead, flat nasal bridge, epicanthic folds, tented upper lip, and smooth philtrum (Fig 1).

EEG showed abnormal sharp waves and spikes firing from centro-temporal areas of brain. MRI brain was normal. Whole Exon Sequencing (WES) utilizing Centoxome Solo Method revealed that Yahia is harboring a heterozygous deletion involving exons1-2 of the *MEF2C* gene (CENTOGEN THE RARE DISEASE COMPANY-Germany; Sample ID 1871427).

Figure 1: Subtle dysmorphic features and stereotypic hand movement in a child diagnosed with (MEF2 C) mutation syndrome

DISCUSSION

The *MEF2C* gene is located in the 5q14.3 region, and is a member of the *MEF2* transcription proteins family [7]. The *MEF2C* factor is classified as a neurogenic and antiapoptotic signaling molecule playing a significant role in regulating function a number of cortical excitatory and inhibitory synapses [8], and in enhancing survival as well as differentiation of postsynaptic dendrites [9]. Correlating to the neuronal expression of *MEF2C*, neurological features including global developmental delay, impaired language function, early hypotonia, limited walking and seizure, are common among affected children [8].

Moreover, Patients with *MEF2C* exhibit several other clinical presentations such as, autistic features, stereotypic behavior, particularly hand flapping, clapping, mouthing, head rocking, and hand biting [10]. Furthermore, other commonly reported symptoms are episodic hyperventilation, tendency to recurrent infections, constipation, and ametropia [2]. Additionally, *MEF2C* is also expressed in muscle, which might explain the phenotypes of hypotonia, heart complications, gastrointestinal issues like constipation, and delayed cross motor skills [11].

MEF2C deficiency syndrome remained under diagnosed, which is in part due to phenotypic features of Rett syndrome spectrum [12]. Certainly, the phenotypic overlap with other neurodevelopmental disorders including Rett syndrome, Angelman Syndrome, and CDKL5 deficiency disorder is clearly documented in the limited literature [10-12]. Interestingly, *MECP2 and CDKL5* genes responsible for Rett syndrome, were found to be downregulated in patients with *MEF2C* deletions indicating a common pathway between the two genes [12, 13]. That might delineate the phenotypic similarities between Rett syndrome and *MEF2C*-related disorders, including seizures, intellectual disability, developmental delay, and stereotypic movements [13]. In contrast to other neurodevelopmental disorders, such as Rett syndrome and Angelman Syndrome, no period of developmental regression or microcephaly are observed in *MEF2C* disorder [2-10].

For diagnosis, *MEF2C* deficiency should be suspected in patients presenting with early hypotonia, delayed in motor skills, limited speech, seizures and stereotypic hand movements [14]. Given the phenotypic overlap with other neurodevelopmental disorders and minor dysmorphism of patients with *MEF2C* syndrome, molecular mutational analysis appears to be the key step for confirming diagnosis [15]. Of note, there is currently no approved therapy that can specifically target mutated *MEF2C* gene, though preclinical studies showed a hope for the Gene Therapy [16]. A multidisciplinary approach addressing the complications/ manifestations is therefore only available option for the management of affected patients.

CONCLUSION

To the best of our knowledge, we report the first case of confirmed *MEF2C* syndrome in Libyan community. *MEF2C* deficiency is a newly emerging neurodevelopmental disorder, and shares common clinical features with Rett Syndrome. It should be therefore considered in patients presenting with global developmental delay, particularly if exhibiting autisitic features and stereotypic behaviors.

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